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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: Hyperlipidemia Combined
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Name of Sponsor/Company:
 Fournier Laboratories Ireland Ltd.

Title of Study: A randomised, double-blind study comparing the efficacy and safety of 145 mg NanoCrystal[®] fenofibrate, 10 mg ezetimibe and their combination in patients with type IIb dyslipidemia and features of the metabolic syndrome.
 Protocol No.: CLF178P 04 01

Coordinating Investigators:
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Study Centers: Patients were treated across 35 investigational centers: 11 in Belgium, 11 in France and 13 in Germany.

Publication (reference): none.

Study Period: 17 DEC 2004 (First Subject First Visit) – 07 APR 2006 (Last Subject Last Visit)	Phase of Development: IIIb
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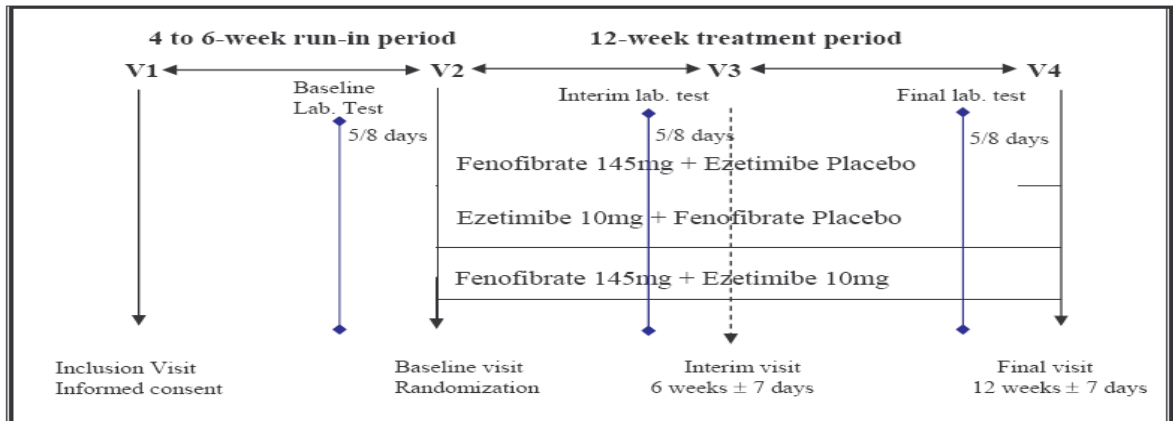
Objectives:
Primary Objective: to demonstrate, in patients with type IIb dyslipidemia and features of the metabolic syndrome (MetS), the clinical advantage of 145 mg NanoCrystal[®] fenofibrate over 10 mg ezetimibe on plasma triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) levels.
Secondary Objectives:

- to compare the efficacy of the 2 monotherapies and the combined therapy from baseline to 12 weeks of treatment on total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, TG, non-HDL-C, LDL size, Remnant-Like Particle Cholesterol (RLP-C), apolipoprotein (Apo) AI, ApoAII, ApoB, high sensitive C-reactive protein (hsCRP), fasting plasma glucose (FPG), insulin, and Homeostasis Model Assessment - Insulin Resistance (HOMA-IR) index,
- to assess the safety of 145 mg NanoCrystal[®] fenofibrate, 10 mg ezetimibe and combined therapy after 12 weeks of treatment.

Methodology:
 This study was a prospective, multicenter, randomized, double-blind, 3-parallel arm, comparative study. The study design is presented below.

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Number of Subjects (Planned and Analyzed): Planned: 62 patients randomized in each treatment group.

Analyzed: Included: 456, Randomized: 181, Treated (Full Analysis Set [FAS]): 180, 60 in each treatment group. Per Protocol Set (PPS): 163: 53 in the fenofibrate group, 55 in the ezetimibe group, 55 in the fenofibrate + ezetimibe group.

Diagnosis and Main Criteria for Inclusion:

Patients presenting with type IIb dyslipidemia as evidenced by LDL-C \geq 160 mg/dL (\geq 4.13 mmol/L), TG \geq 150 mg/dL (\geq 1.71 mmol/L) and \leq 400 mg/dL (\leq 4.57 mmol/L), and with at least 2 of the following 4 MetS criteria according to NCEP-ATP III.

- waist circumference: men $>$ 102 cm, women $>$ 88 cm,
- HDL-C: men $<$ 40 mg/dL ($<$ 1.03 mmol/L) and women $<$ 50 mg/dL ($<$ 1.29 mmol/L),
- blood pressure \geq 130 / \geq 85 mmHg,
- FPG \geq 110 mg/dL (\geq 6.11 mmol/L).

Test Product, Dose and Mode of Administration:

Fenofibrate: 145 mg Nanocrystal® fenofibrate tablets. 1 tablet/day in the evening with or without meal. Oral route.

Duration of Treatment: 12 \pm 1 weeks.

Reference Therapy, Dose and Mode of Administration:

Ezetimibe: 10 mg overencapsulated tablets. 1 capsule/day in the evening with or without meal. Oral route.

Criteria for Evaluation:

Primary Efficacy Criteria: % change in fasting TG and in fasting HDL-C between baseline and end of treatment.

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Secondary Efficacy Criteria: absolute and % change between baseline and end of treatment in lipids and related parameters, apolipoproteins, glycemic control parameters and hsCRP.

Safety: adverse events (AEs), blood chemistry tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (Gamma-GT), total bilirubin, creatine kinase (CK), serum creatinine, urea, uric acid, hematology: red blood cells (RBC), hemoglobin, hematocrit, white blood cells (WBC) and differential counts, 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 superiority of fenofibrate over ezetimibe using an ANCOVA with baseline value and gender (stratification factor) as covariates.

Complementary analyses on the primary efficacy criteria including (1) same analysis as the main efficacy analysis on PPS, (2) exploration of the (treatment*country) interaction term, (3) exploration of the (treatment*gender) interaction term.

The secondary efficacy analyses, conducted on FAS and PPS, included:

- the same ANCOVA model as for the main efficacy analysis: on % changes in lipids, related parameters and apolipoproteins, on % changes in LDL-C according to TG baseline levels (< 3.1 mmol/L and ≥ 3.1 mmol/L), on absolute changes from baseline in FPG, on Log(end-of-treatment values) of fasting insulin, with Log(baseline value) and gender as covariates, on ranks of absolute changes from baseline in HOMA-IR with rank baseline value and gender as covariates.
- descriptive statistics of hsCRP, on all FAS patients and on patients with baseline hsCRP ≤ 2 mg/L / > 2 mg/L.

Post-hoc efficacy analyses consisted of: (1) the exploration of the (treatment*gender) interaction term for lipids and related parameters, apolipoproteins and glycemic control parameters, (2) analysis of hsCRP using the ANCOVA model used for lipids, with exploration of the (treatment*gender) interaction term, (3) analysis of MetS.

The safety analyses, conducted on FAS and in men and women separately, included descriptive statistics of number of AEs, number and % of patients who experienced AEs, summary statistics of blood chemistry and hematology parameters, incidence of abnormal values, scatterplots of worst values on treatment versus baseline values, descriptive statistics of vital signs and anthropometric measurements.

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Summary

Demographic and Other Baseline Characteristics

In FAS, women and men were in equal proportion, 99.4% of the patients were Caucasian, the mean age was 56 years. BMI was ≥ 30 kg/m² in 43.3% of the patients, with a mean value of 30.2 kg/m². The predominant MetS criteria were abnormal TG (100%), increased waist circumference (97.8%) and blood pressure (96.7%). The other 2 MetS criteria were less frequent: elevated FPG (16.7%) and low HDL-C (32.8%).

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Mean with associated SD and median values (mmol/L) of lipids and related parameters at baseline in FAS are presented below.

TG	HDL-C	TC	LDL-C	non-HDL-C	LDL-C/HDL-C	TC/HDL-C	LDL size (A)	RLP-C
2.61 (0.76)	1.32 (0.32)	7.48 (0.90)	5.03 (0.79)	6.16 (0.82)	4.00 (1.03)	5.91 (1.26)	232.3 (4.6)	0.61 (0.38)
2.35	1.26	7.28	4.85	6.01	3.81	5.69	233.0	0.48

The median TG value was close to the limit between borderline-high TG and high TG (2.29 mmol/L) according to the NCEP-ATP III classification. Mean and median HDL-C values were in the low-risk range. Mean and median TC values were in the high range, mean and median LDL-C values were close to the limit between the high range and the very-high range (4.90 mmol/L).

Mean with associated SD and median values of apolipoproteins (g/L), glycemic control parameters (FPG: mmol/L, insulin: mU/L) and hsCRP (mg/L) at baseline in FAS are presented below.

Apolipoproteins				Glycemic control parameters			Inflammation
ApoAI	ApoAII	ApoB	ApoB/ApoAI	FPG	Insulin	HOMA-IR	hsCRP
1.47 (0.25)	0.35 (0.06)	1.46 (0.21)	1.02 (0.22)	5.45 (0.73)	10.7 (7.3)	2.66 (2.04)	2.87 (2.07)
1.43	0.34	1.44	0.99	5.50	8.4	2.02	2.28

Mean and median values of ApoAI and ApoAII were within the laboratory reference range, mean and median values of ApoB were above the upper limit. The ApoB/ApoAI ratio was close to 1. Mean and median values of FPG and insulin were within the laboratory reference range. FAS patients were nearly equally divided between hsCRP levels ≤ 2 mg/L (47.3%) and hsCRP > 2 mg/L (52.7%).

Subgroups at Baseline

Women / Men: There were proportionally more HDL-C values below the cut-off used in the MetS definition (1.29 mmol/L in women and 1.03 mmol/L in men) among women (46.6%) than among men (19.6%). Mean values of LDL-C/HDL-C ratio and TC/HDL-C ratio were slightly higher in men than in women. There were no meaningful differences between genders for the other efficacy parameters.

TG < 3.1 mmol/L and ≥ 3.1 mmol/L: mean values of non-HDL-C, RLP-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, ApoB and ApoB/ApoAI ratio were higher in patients with TG ≥ 3.1 mmol/L than in patients with TG < 3.1 mmol/L, while the opposite was observed for mean values of HDL-C and ApoAI. Plasma insulin and HOMA-IR tended to be higher in the patients with TG ≥ 3.1 mmol/L than in those with TG < 3.1 mmol/L. There were no meaningful differences between the 2 subgroups with respect to FPG and hsCRP.

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Efficacy Results:

Primary Analysis

Triglycerides

Efficacy was evaluated as intent to treat on FAS. Descriptive statistics for TG levels at baseline and at end of treatment and LS-Means of % change at end of treatment from baseline are presented below.

TG (mmol/L) - FAS		Fenofibrate	Ezetimibe	Fenofibrate + Ezetimibe
Lab. ref. range: W: [0.2-1.25] M: [0.3-1.75]		(N=60)	(N=60)	(N=60)
	n	58	56	59
Baseline	Mean (SD), median	2.52 (0.71), 2.25	2.57 (0.70), 2.39	2.77 (0.87), 2.57
	Geometric mean	2.44	2.49	2.65
End of treatment	Mean (SD), median	1.58 (0.87), 1.33	2.25 (0.85), 2.06	1.63 (0.62), 1.43
	Geometric mean	1.43	2.11	1.53
Change at end of treatment	Mean (SD), median	-0.93 (0.70), -1.01	-0.32 (0.82), -0.38	-1.14 (0.76), -1.05
% change at end of treatment	Mean (SD), median	-37.7 (22.9), -43.8	-10.1 (29.5), -14.9	-39.2 (21.1), -41.2
	Back transf. mean ^a	-41.2	-15.1	-42.4
LS-M % change	Estimate (SE), 95% CI	-38.3 (3.2) [-44.7; -32.0]	-10.4 (3.3) [-16.9; -4.0]	-38.3 (3.2) [-44.7; -32.0]
Contrast fenofibrate - ezetimibe		-27.9 (4.6) [-37.0 ; -18.9], p < 0.001		

^a Back-transformed mean (%) = 100*(Exp(Mean of {Log(end-of-treatment Values) - Log(Baseline Values)}) - 1). LS-M: LS-Mean.

The ANCOVA model, on either raw values or Log-transformed values, did not reach statistical significance for the gender covariate. The primary objective of the study was reached with respect to changes in TG: the clinical advantage of 145 mg NanoCrystal[®] fenofibrate over 10 mg ezetimibe on plasma TG levels was demonstrated.

HDL-C

Descriptive statistics for HDL-C levels at baseline and at end of treatment and LS-Means of % changes at end of treatment from baseline are presented below.

HDL-C (mmol/L) - FAS		Fenofibrate	Ezetimibe	Fenofibrate + Ezetimibe
Lab. ref. range: W: [0.96-2.09] M: [0.9-1.71]		(N=60)	(N=60)	(N=60)
	n	58	56	59
Baseline	Mean (SD), median	1.34 (0.37), 1.26	1.26 (0.25), 1.23	1.33 (0.31), 1.32
	Geometric mean	1.30	1.24	1.29
End of treatment	Mean (SD), median	1.43 (0.40), 1.39	1.29 (0.31), 1.20	1.46 (0.33), 1.44
	Geometric mean	1.38	1.26	1.42
Change at end of treatment	Mean (SD), median	0.09 (0.22), 0.07	0.03 (0.23), -0.02	0.13 (0.26), 0.12
% change at end of treatment	Mean (SD), median	7.3 (17.0), 5.7	2.8 (18.2), -1.3	11.1 (19.5), 10.6
	Back transf. mean ^a	6.0	1.4	9.6

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LS-M % change	Estimate (SE), 95% CI	7.9 (2.3) [3.3 ; 12.5]	2.2 (2.4) [-2.5 ; 6.9]	11.5 (2.3) [6.9 ; 16.0]	
Contrast fenofibrate - ezetimibe		5.7 (3.3) [-0.9 ; 12.3], p = 0.088			

^a Back-transformed mean (%) = 100*(Exp(Mean of {Log(end-of-treatment Values) - Log(Baseline Values)}) - 1). LS-M: LS-Mean.

The ANCOVA model, on either raw values or Log-transformed values, reached statistical significance for the gender covariate. The primary objective of the study was not reached with respect to changes in HDL-C. The difference of 5.7% between the 2 treatments corresponded to a moderate clinical advantage of 145 mg NanoCrystal[®] fenofibrate over 10 mg ezetimibe on plasma HDL-C levels.

Complementary Analyses on the Primary Criteria

The PPS analysis confirmed the FAS analysis with respect to TG reduction, LS-Means: -41.9% with fenofibrate and -10.6% with ezetimibe. Regarding HDL-C, the PPS analysis revealed a statistically significant difference (p = 0.026) between fenofibrate (+8.6%) and ezetimibe (+1.2%). The increase was 12.3% with fenofibrate + ezetimibe.

The reduction in TG with fenofibrate and fenofibrate + ezetimibe was between 5 and 8% smaller in Belgium than in France and Germany, 2 countries where the reduction was much the same. The ANCOVA model did not reach statistical significance for the (treatment*country) interaction term.

The effect of fenofibrate or fenofibrate + ezetimibe on HDL-C showed great variations from one country to the other. The best effect was obtained in Germany, LS-Means: +9.9% and +15.4%, respectively, compared to +6.6% and +7.5% in France and +2.7% and +5.6% in Belgium. The ANCOVA model did not reach statistical significance for the (country*treatment) interaction term.

Fenofibrate alone and fenofibrate + ezetimibe had the same TG-lowering effect in women and in men. The ANCOVA model did not reach statistical significance for the (treatment*gender) interaction term (p = 0.613).

For HDL-C, the ANCOVA model reached statistical significance for the (treatment*gender) interaction term (p = 0.001). In women, changes (LS-Means) were +14.9%, -3.9% and +15.2% with fenofibrate, ezetimibe and fenofibrate + ezetimibe, respectively; in men: +2.0%, +6.7% and +7.8%, respectively (post-hoc analysis).

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Secondary Analyses

Main Lipids and Related Parameters

LS-Means with associated SE and 95% CI of % changes in main lipids and related parameters in FAS patients are presented below.

Main lipids and related parameters	Fenofibrate (N=60)	Ezetimibe (N=60)	Fenofibrate + Ezetimibe (N=60)
TC	-18.9 (1.3) [-21.4 ; -16.3]	-17.1 (1.3) [-19.8 ; -14.5]	-27.9 (1.3) [-30.4 ; -25.3] ^{ab}
Calculated LDL-C	-22.4 (1.6) [-25.6 ; -19.1]	-22.8 (1.7) [-26.1 ; -19.6]	-36.2 (1.6) [-39.4 ; -33.0] ^{ab}
Non-HDL-C	-24.8 (1.6) [-28.0 ; -21.6]	-20.9 (1.7) [-24.1 ; -17.6]	-36.2 (1.6) [-39.4 ; -33.0] ^{ab}
LDL-C/HDL-C ratio	-26.3 (2.1) [-30.4 ; -22.2]	-22.5 (2.1) [-26.6 ; -18.3]	-41.7 (2.0) [-45.7 ; -37.7] ^{ab}
TC/HDL-C ratio	-23.0 (1.8) [-26.6 ; -19.4] ^c	-17.0 (1.9) [-20.7 ; -13.3]	-34.2 (1.8) [-37.7 ; -30.6] ^{ab}
RLP-C	-30.7 (5.6) [-41.6 ; -19.7]	-17.3 (5.8) [-28.7 ; -5.9]	-36.2 (5.4) [-46.9 ; -25.5] ^b
LDL size	1.9 (0.2) [1.5 ; 2.4] ^c	0.7 (0.2) [0.2 ; 1.2]	2.1 (0.2) [1.7 ; 2.6] ^b

^a difference (fenofibrate + ezetimibe) - fenofibrate statistically significant.

^b difference (fenofibrate + ezetimibe) - ezetimibe statistically significant.

^c difference fenofibrate – ezetimibe statistically significant.

Results for TG and HDL-C are presented with the results of the primary analysis. The reduction in TG with fenofibrate + ezetimibe was the same as with fenofibrate alone (LS-Mean: -38.3%). The increase in HDL-C with fenofibrate + ezetimibe was 11.5% (LS-Mean), which was not statistically different from the increase with fenofibrate alone (+7.9%).

Fenofibrate and ezetimibe were equally effective in reducing TC, LDL-C, non-HDL-C and LDL-C/HDL-C ratio. Fenofibrate was better than ezetimibe in reducing the TC/HDL-C ratio and in increasing LDL size.

Fenofibrate + ezetimibe was better than either fenofibrate or ezetimibe in reducing TC, LDL-C, non-HDL-C, LDL-C/HDL-C ratio and TC/HDL-C ratio, and better than ezetimibe in reducing RLP-C and in increasing LDL size. Fenofibrate + ezetimibe was not better than fenofibrate in increasing LDL size. The PPS analyses provided the same results as the FAS analyses, except for non-HDL-C for which the difference between fenofibrate (-26.0%) and ezetimibe (-20.7%) was statistically significant (p = 0.026), as well as for RLP-C: -33.9% with fenofibrate and -17.4% with ezetimibe (p = 0.042).

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Apolipoproteins

LS-Means with associated SE and 95% CI of % changes in apolipoproteins in FAS patients are presented below.

Apolipoproteins	Fenofibrate (N=60)	Ezetimibe (N=60)	Fenofibrate + Ezetimibe (N=60)
ApoAI	5.1 (1.6) [2.0 ; 8.1] ^a	0.2 (1.6) [-3.0 ; 3.4]	7.9 (1.5) [4.9 ; 11.0] ^b
ApoAII	21.2 (2.0) [17.3 ; 25.0] ^a	2.7 (2.0) [-1.3 ; 6.7]	24.2 (1.9) [20.5 ; 28.0] ^b
ApoB	-24.5 (1.6) [-27.6 ; -21.4] ^a	-18.7 (1.6) [-21.9 ; -15.5]	-33.3 (1.5) [-36.3 ; -30.3] ^{b c}
ApoB/ApoAI ratio	-27.0 (1.8) [-30.6 ; -23.4] ^a	-17.7 (1.9) [-21.5 ; -14.0]	-37.5 (1.8) [-41.0 ; -34.0] ^{b c}

^adifference fenofibrate – ezetimibe statistically significant.

^bdifference (fenofibrate + ezetimibe) - ezetimibe statistically significant.

^cdifference (fenofibrate + ezetimibe) - fenofibrate statistically significant.

Ezetimibe had no effect on ApoAI and ApoAII. Fenofibrate and fenofibrate + ezetimibe were equally effective in increasing ApoAI and ApoAII. The 3 treatments reduced ApoB and the ApoB/ApoAI ratio; fenofibrate being better than ezetimibe, and fenofibrate + ezetimibe better than both fenofibrate and ezetimibe. The PPS analyses provided same results as the FAS analyses. The ANCOVA model on ApoAI, ApoAII and ApoB/ApoAI ratio reached statistical significance for the gender covariate.

Post-hoc Analyses on Lipids, Related Parameters and Apolipoproteins

They consisted in analyzing the treatment-by-gender interaction. This was found to be statistically significant for LDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, ApoAI, ApoAII, ApoB and ApoB/ApoAI ratio. These parameters were therefore analyzed in women and men separately. The LS-Means of % changes at end of treatment from baseline and the statistical significance are presented below.

Lipids and apolipoproteins	Women			Men		
	Fenofibrate	Ezetimibe	Fenofibrate + Ezetimibe	Fenofibrate	Ezetimibe	Fenofibrate + Ezetimibe
Calculated LDL-C	-28.4 ^{a''}	-20.6	-37.2 ^{b' c}	-17.3 ^{a''}	-24.4	-35.0 ^{b c}
Non-HDL-C	-29.8 ^a	-18.4	-36.7 ^{b' c}	-20.5	-22.8	-35.6 ^{b c}
LDL-C/HDL-C ratio	-36.5 ^a	-17.2	-43.8 ^c	-17.7 ^{a''}	-26.3	-39.5 ^{b c}
TC/HDL-C ratio	-29.8 ^a	-12.4	-35.2 ^c	-17.1	-20.6	-33.1 ^{b c}
ApoAI	10.2 ^a	-4.8	11.7 ^c	0.7	3.6	4.0
ApoAII	29.6 ^a	-0.4	29.5 ^c	13.8 ^{a'}	4.4	19.1 ^c
ApoB	-29.6 ^a	-17.1	-34.5 ^c	-20.3	-19.4	-32.0 ^{b c}
ApoB/ApoAI ratio	-34.9 ^a	-12.9	-40.8 ^c	-20.3	-21.0	-34.2 ^{b c}

a = p < 0.001, a' = p < 0.01, a'' = p < 0.05 for statistically significant differences between fenofibrate and ezetimibe.

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b = p < 0.001, b' = p < 0.05 for statistically significant differences between (fenofibrate + ezetimibe) and fenofibrate.

c = p < 0.001 for statistically significant differences between (fenofibrate + ezetimibe) and ezetimibe.

In women, fenofibrate was better than ezetimibe in decreasing LDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, ApoB and ApoB/ApoAI ratio and in increasing ApoAI and ApoAII. The co-administration was better than both fenofibrate and ezetimibe on LDL-C and non-HDL-C, and better than ezetimibe but not than fenofibrate on LDL-C/HDL-C ratio, TC/HDL-C ratio, ApoB and ApoB/ApoAI ratio and on ApoAI and ApoAII.

In men, ezetimibe was better than fenofibrate on LDL-C and LDL-C/HDL-C ratio, while fenofibrate was better than ezetimibe on ApoAII. The co-administration was better than both fenofibrate and ezetimibe on LDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, ApoB and ApoB/ApoAI ratio, and better than ezetimibe on ApoAII.

Glycemic Control Parameters

LS-Means (SE) and 95% CI of changes in glycemic control parameters in FAS patients are presented below.

Glycemic control		Fenofibrate (N=60)	Ezetimibe (N=60)	Fenofibrate + Ezetimibe (N=60)
FPG (LS-Means of changes)		0.01 (0.10) [-0.19 ; 0.20]	-0.04 (0.10) [-0.24 ; 0.15]	0.19 (0.10) [0.00 ; 0.39]
Insulin mU/L	Baseline ^a	8.4	8.4	8.6
	End of treatment ^a	9.0	9.3	8.9
	End of treatment ^b	8.8 [7.6 ; 10.2]	9.6 [8.3 ; 11.1]	9.1 [7.9 ; 10.5]
HOMA -IR	Baseline ^a	1.93	2.06	2.08
	End of treatment ^a	2.14	2.05	2.18
	Changes ^c	82.5 (6.3) [70.0 ; 95.0]	88.1 (6.3) [75.6 ; 100.6]	80.4 (6.4) [67.8 ; 93.0]

^a medians, ^b LS-Means of end-of-treatment values after Log-transformation, ^c LS-Means of ranks of absolute changes.

FPG, insulin and HOMA-IR remained unchanged in the 3 treatment groups. The PPS analyses provided same results as the FAS analyses.

Inflammation

Changes in hsCRP were highly variable. LS-Means of % changes were -27.8% with fenofibrate, -10.2% with ezetimibe and -25.9% with fenofibrate + ezetimibe. In the patients with hsCRP > 2 mg/L at baseline, the median % changes were -42.7% with fenofibrate, -17.4% with ezetimibe and -28.8% with fenofibrate + ezetimibe. In those with hsCRP ≤ 2 mg/L at baseline, a reduction was observed with fenofibrate + ezetimibe only (median: -23.1%).

Metabolic Syndrome

The analysis of MetS was a post-hoc analysis performed on the FAS patients who had data for the 5 criteria defined by NCEP-ATP III at V4 (n = 55 or 56 by treatment group). At V4, normalization was achieved in 69.6% of the patients on fenofibrate, 32.7% of the patients on ezetimibe and 58.2% of the patients on fenofibrate + ezetimibe. Decrease in TG and in blood pressure and increase in HDL-C were the main contributors to normalization and to differences

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between treatments. The differences between fenofibrate and ezetimibe and between (fenofibrate + ezetimibe) and ezetimibe were statistically significant with respect to the percentages of patients who had normal TG or normal HDL-C at V4. The same was true for women, while for men the 2 differences were statistically significant for TG only. The number and percentage of patients, by gender, who had no longer MetS at V4 and with change in TG, HDL-C and blood pressure from abnormal to normal between baseline and V4 are presented below.

MetS	Women			Men		
	Fenofibrate	Ezetimibe	Fenofibrate + Ezetimibe	Fenofibrate	Ezetimibe	Fenofibrate + Ezetimibe
n	27	25	25	29	30	30
MetS normalization	21/27 (77.8%)	4/25 (16.0%)	15/25 (60.0%)	18/29 (62.1%)	14/30 (46.7%)	17/30 (56.7%)
TG^a	21/27 (77.8%)	4/25 (16.0%)	16/25 (64%)	20/29 (69.0%)	11/30 (36.7%)	20/30 (66.7%)
HDL-C^b	7/12 (58.3%)	1/14 (7.1%)	6/11 (54.6%)	3/5 (60.0%)	3/6 (50.0%)	3/6 (50.0%)
Blood pressure^c	6/25 (24.0%)	6/24 (25.0%)	10/25 (40.0%)	3/28 (10.7%)	7/30 (23.3%)	13/28 (46.4%)

^a change from ≥ 1.71 mmol/L to < 1.71 mmol/L in women and in men.

^b change from < 1.29 mmol/L to ≥ 1.29 mmol/L in women and from < 1.03 mmol/L to ≥ 1.03 mmol/L in men.

^c change from $\geq 130 / \geq 85$ mmHg to $< 130 / < 85$ mmHg in women and in men.

In women, the marked difference in normalization rate between fenofibrate and ezetimibe was due to differences in effects on TG and on HDL-C. Fenofibrate had a significant effect on HDL-C in women who had low baseline levels. In men the difference was less pronounced between fenofibrate and ezetimibe due to less frequent low HDL-C levels at baseline. In both women and men, normalization of blood pressure was more frequent with the co-administration than with either monotherapy.

Safety Results:

Deaths

There were no deaths during the study.

Serious Adverse Events (SAEs)

Three (3) SAEs, not related to study treatment, were reported in 2 patients in the fenofibrate + ezetimibe group: strumectomy in 1 patient and detection of prostate carcinoma and radical prostatectomy in the other.

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All Adverse Events (AEs)

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

	Fenofibrate	Ezetimibe	Fenofibrate + Ezetimibe
All AEs	15 (25.0%)	13 (21.7%)	19 (31.7%)
AEs related ^a	6 (10.0%)	4 (6.7%)	10 (16.7%)

^a unknown or reasonable suspect causal relationship with study drug.

Four (4) patients, 2 patients in the fenofibrate group, 1 patient in the ezetimibe group and 1 patient in the fenofibrate + ezetimibe group, were prematurely withdrawn from the study because of AEs. Of these AEs, urticaria in 1 patient in the fenofibrate group, pruritus in the patient in the fenofibrate + ezetimibe group and generalized pruritus, headache and nausea in the patient in the ezetimibe group were considered as related to study treatment. Gastroenteritis in the other patient in the fenofibrate group was considered as not related to study treatment.

Abnormal laboratory investigations including increase in CK, in liver enzymes and in blood creatinine were the most frequent AEs related to study treatment in the fenofibrate group (3 patients) and in the fenofibrate + ezetimibe group (6 patients). The other AEs related to study treatment were infrequent, being reported in no more than 1 patient, and roughly equally distributed across the 3 treatment groups.

Clinical Laboratory Evaluation

Three (3) patients were found to have clinically significant changes in laboratory tests. In the fenofibrate group, 1 patient was found to have an increase in ALT from normal to > 3 times the upper limit of normal (ULN) (4.6 times) and 1 patient an increase in creatinine from normal to above the protocol pre-defined limits (110 µmol/L in women and 135 µmol/L in men). In the fenofibrate + ezetimibe group, 1 patient was found to have an increase in CK from 1.7 times the ULN to 5.6 times the ULN.

The incidence of ALT increase from normal to the [ULN - 3*ULN] range was 17% in the fenofibrate group, 23% in the ezetimibe group and 33% in the fenofibrate + ezetimibe group. For AST, the figures were 13%, 5% and 28%, respectively. The incidence of CK increase from normal to the [ULN - 3*ULN] range was 12% in the fenofibrate group, 15% in the ezetimibe group and 8% in the fenofibrate + ezetimibe group. The incidence of increases in creatinine from normal to abnormal, but below the protocol pre-defined limits, was 27% in the fenofibrate group, 8% in the ezetimibe group and 42% in the fenofibrate + ezetimibe group. Two (2) patients in the fenofibrate group and 4 patients in the fenofibrate + ezetimibe group were found to have an absolute change in creatinine > 30 µmol/L between baseline and the end of the study.

Alkaline phosphatase decreased similarly in the fenofibrate group (mean: from 76 IU/L to 61 IU/L) and in the fenofibrate + ezetimibe group (mean: from 74 IU/L to 57 IU/L). Uric acid

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decreased by 22% in these 2 groups. Serum creatinine and urea tended to increase in the fenofibrate group and in the fenofibrate + ezetimibe group: +7.4 to +9.8 $\mu\text{mol/L}$ for creatinine and +0.35 mmol/L for urea. Alkaline phosphatase, creatinine, urea and uric acid did not change in the ezetimibe group.

There were minimal changes in hematological parameters in the fenofibrate group and in the fenofibrate + ezetimibe group, with a small decrease in hemoglobin (median: -5 g/L and -6 g/L), in WBC numbers (median: $-0.17 \times 10^9/\text{L}$ and $-0.21 \times 10^9/\text{L}$) and a small increase in platelet numbers (median: $+24 \times 10^9/\text{L}$ and $+27 \times 10^9/\text{L}$). No changes in these parameters were observed in the ezetimibe group.

Vital Signs and Anthropometric Measurements

Heart rate remained unchanged in the 3 treatment groups during the study. Between baseline and end of treatment, the mean SBP values decreased from 141.5 to 134.0 mmHg in the fenofibrate group, from 143.2 to 135.6 mmHg in the ezetimibe group and from 142.1 to 130.8 mmHg in the fenofibrate + ezetimibe group. The mean DBP values decreased from 87.4 to 78.4 mmHg, from 87.3 to 79.4 mmHg and from 87.6 to 79.7 mmHg, respectively. Body weight, BMI and waist circumference remained unchanged in the 3 treatment groups.

Safety in Women and Men Separately

There was no meaningful difference between genders in the number of patients who experienced at least 1 AE considered as related to study treatment. The 4 patients who were prematurely withdrawn because of AEs were women. In the groups treated with fenofibrate, Gamma-GT decreased in men only: from 72 to 41 IU/L (means) in the fenofibrate group and from 97 to 69 IU/L (means) in the fenofibrate + ezetimibe group. Non-clinically significant changes in transaminases were more frequent in women than in men: 22 patients compared to 11 patients for ALT and 15 patients compared to 10 patients for AST. There were no meaningful differences between women and men with respect to changes in CK from normal to the $[\text{ULN} - 3 \times \text{ULN}]$ range and in creatinine from normal to abnormal but below the protocol pre-defined limits (i.e. 110 $\mu\text{mol/L}$ in women and 135 $\mu\text{mol/L}$ in men).

Differences in the ezetimibe group were observed for WBC: increase in women (mean: $+0.7 \times 10^9/\text{L}$) and decrease in men (mean: $-0.35 \times 10^9/\text{L}$) and for platelets: decrease in men only (mean: $-18 \times 10^9/\text{L}$).

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