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CLINICAL STUDY REPORT SYNOPSIS

Clinical Report No.:	Final version	**Protocol No.:**	FENOPRA-III-06-1
		EudraCT No.:	2006-006557-28
Date of Issue:	May 13th, 2009		
Study Title:	**A PHASE III, FOUR-ARMED,RANDOMIZED, DOUBLE BLIND, PARALLEL STUDY TO COMPARE THE EFFICACY AND SAFETY IN TYPE 2 DIABETIC PATIENTS WITH COMBINED HYPERLIPIDEMIA OF A 12-WEEK ADMINISTRATION OF FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION VERSUS SIMVASTATIN 20MG IN PATIENTS WITHOUT CARDIOVASCULAR DISEASE (CVD) (GROUP 1) AND OF FENOFIBRATE 160 MG/PRAVASTATIN 40MG COMBINATION+EZETIMIBE 10MG VERSUS SIMVASTATIN 20MG+EZETIMIBE 10MG IN PATIENTS WITH CVD (GROUP 2), FOLLOWED BY A 12-WEEK SAFETY PHASE OF FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION IN GROUP 1 AND FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION+EZETIMIBE 10MG IN GROUP 2.**		
Abbreviated Title	PREFED		
Drug Name:	Fenofibrate 160 mg/Pravastatin 40 mg combination		
Indication / Purpose:	Combined hyperlipidemia		
Methodology:	Multicentre, double blind, controlled, 4-arm randomized parallel study, in two populations of patients stratified according to their cardiovascular risk (high cardiovascular risk / very high cardiovascular risk).		
Drug Development Phase:	III		
Country:	France, Norway, Romania, Poland, Hungary, Germany		
Coordinating Investigator:	Michel FARNIER, MD, PhD Point Médical Rond Point de la Nation 21000 Dijon		
First Patient First Visit:	June 18th, 2007		
Last Patient Last Visit:	December 22nd, 2008		
Sponsor Signatory:	Laboratoires SMB S.A. Rue de la Pastorale, 26-28 1080 Brussels, Belgium		

Name of Sponsor/Company: Laboratoires SMB S.A.	Individual Study Table Referring to Module 5 of the dossier Volume: Page:	**(For National Authority Use only)**
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Title of Study: PREFED

A PHASE III, FOUR-ARMED, RANDOMIZED, DOUBLE BLIND, PARALLEL STUDY TO COMPARE THE EFFICACY AND SAFETY IN TYPE 2 DIABETIC PATIENTS WITH COMBINED HYPERLIPIDEMIA OF A 12-WEEK ADMINISTRATION OF FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION VERSUS SIMVASTATIN 20MG IN PATIENTS WITHOUT CARDIOVASCULAR DISEASE (CVD) (STRATUM 1) AND OF FENOFIBRATE 160 MG/PRAVASTATIN 40MG COMBINATION+EZETIMIBE 10MG VERSUS SIMVASTATIN 20MG+EZETIMIBE 10MG IN PATIENTS WITH CVD (STRATUM 2), FOLLOWED BY A 12-WEEK SAFETY PHASE OF FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION IN STRATUM 1 AND FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION+EZETIMIBE 10MG IN STRATUM 2.

Study Center/Investigator:

78 centers were planned for recruitment: 24 in France, 8 in Norway, 16 in Romania, 10 in Poland, 11 in Hungary and 9 in Germany.

73/78 centers were active and enrolled at least one patient (20 in France, 8 in Norway, 16 in Romania, 10 in Poland, 10 in Hungary and 9 in Germany). 65 of these 73 centers randomized at least one patient : 18 in France, 7 in Norway, 16 in Romania, 8 in Poland, 10 in Hungary and 6 in Germany.

Publication (Reference):
NA.

Study Period:	**Phase of Development:**
18/06/2007 (First Patient First Visit) - 22/12/2008 (Last Patient Last Visit).	Phase III

Objectives:

1) to demonstrate the superiority of the efficacy of Fenofibrate 160 mg/Pravastatin 40 mg combination versus Simvastatin 20 mg in type 2 diabetic patients without cardiovascular disease and with combined hyperlipidemia and to describe the safety of the combination,

2) to demonstrate the superiority of the efficacy of Fenofibrate 160 mg/Pravastatin 40 mg combination + Ezetimibe 10 mg versus Simvastatin 20 mg + Ezetimibe 10 mg in type 2 diabetic patients with cardiovascular disease and with combined hyperlipidemia and to describe the safety of the Fenofibrate 160 mg/Pravastatin 40 mg combination + Ezetimibe 10 mg.

Primary objective:
To evaluate the mean percent changes in plasma non-HDL cholesterol levels at the end of the efficacy period compared to baseline.

Secondary objectives:

- To assess and compare the evolution of the following lipid parameters: LDL-C, HDL-C, TG and total cholesterol at the end of the efficacy period.
- To assess and compare the evolution of ApoA1 and ApoB levels, and of the ApoB/ApoA1 ratio at the end of the efficacy period.
- To evaluate the changes in hs-CRP levels at the end of the efficacy period.
- To evaluate the changes in fibrinogen values at the end of the efficacy period.
- To evaluate the percentage of patients who achieved the therapeutic goals with regards to non-HDL cholesterol and LDL-C levels at the end of the efficacy period, as defined in the NCEP ATP III.
- To compare the safety profiles of Simvastatin 20 mg and Fenofibrate 160 mg/Pravastatin 40 mg combination with and without Ezetimibe during the 12-week efficacy period, and to describe the safety profile of Fenofibrate 160 mg/Pravastatin 40mg combination with and without Ezetimibe 10 mg during the 12-week safety period.

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Methodology:

This was a randomized, controlled, double-blind, 4-arm parallel study, conducted in two separate strata of diabetic patients stratified according to history of cardiovascular disease (Stratum 1: patients without a history of cardiovascular disease were defined as high cardiovascular risk patients; Stratum 2: patients with a history of cardiovascular disease were defined as very high cardiovascular risk patients)

The planned duration of the study was 31 weeks maximum per patient and included:

- a selection period (7 weeks with a 6-week run in period),
- a 12-week double-blind treatment period,
- a 12-week follow-up period.

During the first week of the selection period, selection criteria were checked and laboratory tests were performed. Patients remained on their lipid-lowering treatment (or remained untreated if they were not previously treated). During the 6 weeks of the run-in period patients who met the selection criteria received one tablet of Simvastatin 20 mg per day. No change in diabetic therapy could occur during the selection period.

A central pre-randomization by-phone system (Interactive Voice Response System : IVRS) was used to randomize the patients at V3 (W0) into 4 double blind groups:

- Patients without cardiovascular disease (high CV risk = stratum 1)
  - 1 group with patients treated with Fenofibrate 160 mg/Pravastatin 40 mg combination per day,
  - 1 group with patients treated with Simvastatin 20 mg per day.
- Patients with cardiovascular disease (very high CV risk = stratum 2)
  - 1 group with patients treated with Fenofibrate 160 mg/Pravastatin 40 mg combination per day + Ezetimibe 10 mg per day,
  - 1 group with patients treated with Simvastatin 20 mg + Ezetimibe 10 mg per day.

Laboratory parameters were measured at the end of the selection period, one week before the randomization. If the laboratory parameters remained within the inclusion criteria and the therapeutic goals in non-HDL-C or LDL-C levels and TG levels were not achieved, the patients were then randomized to the efficacy period.

This efficacy period was followed by an open-label additional 12-week safety period (from W12 to W24) during which patients received the Fenofibrate/Pravastatin combination without Ezetimibe in stratum 1 and with Ezetimibe in stratum 2.

During all periods of the study, patients were asked to continue adequate diet and exercise; patients with controlled hypothyroidism could not alter their treatment throughout the study.

Number of Patients (Planned, Selected, Randomized and Analyzed):

Planned: 240 patients without history of CVD (120 patients in the Fenofibrate 160 mg/Pravastatin 40 mg group, 120 patients in the Simvastatin 20 mg group); 240 patients with history of CVD (120 patients in the Fenofibrate 160 mg/Pravastatin 40 mg + Ezetimibe 10 mg group, 120 patients in the Simvastatin 20 mg + Ezetimibe 10 mg group);

Selected: 1301 patients.

Randomized: 564 patients (291 in the high CV risk stratum, 273 in the very high CV risk stratum).

Treated: 563 patients (291 in the high CV risk stratum, 272 in the very high CV risk stratum).

Safety analysis for the W0-W12 period: 563 patients (291 in the high CV risk stratum, 272 in the very high CV risk stratum).

Safety analysis for the W12-W24 period: 537 patients (281 in the high CV risk stratum, 256 in the very high CV risk stratum).

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ITT efficacy analysis: 555 patients (289 in the high CV risk stratum, 266 in the very high CV risk stratum).

PP analysis: 545 patients (284 in the high CV risk stratum, 261 in the very high CV risk stratum).

Diagnosis and Main Criteria for Inclusion:

Patients:
Men or women aged 18 years and older, with type 2 diabetes and documented hyperlipidemia, with or without a history of CV disease.

Clinical characteristics:
Patients followed a standardized diet for at least 3 months before the selection period and maintained stable throughout the study. Female patients with child-bearing potential had to provide a negative serum pregnancy test at the selection visit and had to use an efficient mean of birth control throughout the study. Patients with a recent acute cardiovascular episode, uncontrolled hypertension, uncontrolled hypothyroidism or uncontrolled diabetes (HbA1c>8.5%) were not included.

Laboratory values prior to randomization:
The non-HDL-C level had to be ≥ 130 mg/dL (3.36 mmol/L) or the LDL-C level had to be ≥ 100 mg/dL (2.6 mmol/L) in patients without a history of CV disease; the non-HDL-C level had to be ≥ 100 mg/dL (2.59 mmol/L) or the LDL-C level had to be ≥ 70 mg/dL (1.8 mmol/L) in patients with a history of CV disease. TG levels had to be ≥ 150 mg/dL (1.7 mmol/L) and ≤ 600 mg/dL (6.8 mmol/L) in the laboratory sample taken one week before the randomization visit. ASAT and ALAT levels had to be ≤ 2 UNL and CPK level had to be ≤ 3 UNL in the laboratory sample taken one week before randomization. For German centers ASAT and ALAT levels had to be ≤ 1.5 UNL and CPK level had to be ≤ 1 UNL. Creatinine clearance had to be ≥ 60 mL/mn (according to Cockroft-Gault formula) and creatinine level had to be lower than 15 mg/L.

Test Product, Dose and Mode of Administration:

- Fenofibrate 160 mg/Pravastatin 40 mg, capsules, one capsule to be taken daily during the evening meal with a glass of water.
- Simvastatin 20 mg (ZOCOR®), blinded, capsule containing a tablet, one capsule to be taken daily during the evening meal with a glass of water.
- Ezetimibe (EZETROL®) 10 mg, tablet, one tablet to be taken daily during the evening meal with a glass of water (for very high CV risk patients).

Duration of Treatment:

- Simvastatin 20 mg daily from W-6 to W0 by all patients.

For patients in the high CV risk stratum :

- Fenofibrate 160 mg/Pravastatin 40 mg daily or Simvastatin 20 mg daily from W0 to W12.
- Fenofibrate 160 mg/Pravastatin 40 mg daily from W12 to W24.

For patients in the very high CV risk stratum :

- Fenofibrate 160 mg/Pravastatin 40 mg + Ezetimibe 10 mg daily or Simvastatin 20 mg + Ezetimibe 10 mg daily from W0 to W12.
- Fenofibrate 160 mg/Pravastatin 40 mg + Ezetimibe 10 mg daily from W12 to W24.

Criteria for Evaluation:

Primary efficacy assessment:

- Mean percent change in non-HDL-C levels from baseline to W12 (the end of the efficacy period)

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Secondary efficacy assessment:

- Mean percent change from baseline to W12 (the end of the efficacy period), from baseline to W6, from baseline to W18 and from baseline to W24 (the end of the study) in other biological test levels (total cholesterol, HDL-C, LDL-C, TG, Apo A1, Apo B, Apo B/Apo A1 ratio, fibrinogen, hs-CRP)
- Percentage of patients with non-HDL-C levels at target at W6, W12 (the end of the efficacy period), W18 and W24 (the end of the study)
- Percentage of patients with LDL-C levels at target at W6, W12 (the end of the efficacy period), W18 and W24 (the end of the study)

Safety parameters:

- Adverse events (AEs)
- Vital signs (weight, waist circumference, SBP, DBP, HR)
- Physical examination (by body system)
- Laboratory evaluation:
  - Haematology (WBC, RBC, hemoglobin, haematocrit and platelets)
  - Biochemical markers (plasma glucose, HbA1c, CPK, ASAT, ALAT, creatinine, creatinine clearance, TSH, total bilirubin, alkaline phosphatase, homocysteine)
  - Increase in transaminase levels
  - Increase in CPK
  - Increase in creatininemia and decrease in creatinine clearance
- Appearance of myopathy/rhabdomyolysis
- Withdrawals or drop-out rate
- Electrocardiogram at W-7 and W12 (the end of the efficacy period)

Statistical Methods:

Handling of missing data:

Missing data post randomization were replaced by the last available value. Missing data at W12 were replaced by the W6 value.

Definitions:

Baseline: (value V2 + value V3)/2. Use of retest value if available.
End point: value at V5, or value at V4, or value at premature termination visit if the patient prematurely discontinued from the study.

Descriptive statistics:

Continuous variables were described in each stratum for each group by the number of documented patients, mean, standard deviation, 95 % two-sided confidence interval (when relevant), range, median and number of missing data.

Binary and categorical variables were described in each stratum and for each group by the frequency and percentage of each modality as well as the number of missing data.

Efficacy analysis:

The study aimed to demonstrate the superiority of the Fenofibrate 160 mg/Pravastatin 40 mg combination over Simvastatin 20 mg. Patients were stratified at entry based on their CV risk. Since the entry criteria, treatment regimens and targets were not homogeneous between the strata, the analyses were conducted separately within the two strata.

The main analysis was conducted on an intent-to-treat basis (ITT), using the 9.1. SAS software (SAS Institute, Cary, NC, USA). The primary endpoint was the mean percent change in non-HDL-C levels from baseline to W12 (the end of the efficacy period) comparing the Fenofibrate 160 mg/Pravastatin 40

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mg combination to Simvastatin 20 mg in each stratum. Change in lipids between baseline and W12 (the end of the efficacy period) were computed as follows: W12 (end of efficacy period) value – baseline value. So a decrease in lipids gave a negative value.

The statistical analyses compared the group receiving the Fenofibrate 160 mg/Pravastatin 40 mg combination to Simvastatin 20 mg in each stratum. In order to test the superiority of Fenofibrate 160 mg/Pravastatin 40 mg combination over Simvastatin 20 mg, tests were one-sided. The α risk was set at 0.025. Changes in non-HDL-C levels were described in each stratum for the two groups. Differences between Fenofibrate 160 mg/Pravastatin 40 mg combination and Simvastatin 20 mg in each stratum were described along with the 97.5% confidence interval. Clinically, a relevant limit of superiority was set at 5% for primary endpoint non-HDL-C.

A generalised linear model was built with treatment as explaining variable and baseline as covariate (ANCOVA). Effect size was computed as difference between LSmeans for the comparison of Fenofibrate 160 mg/Pravastatin 40 mg versus Simvastatin 20 mg in each stratum and one sided 97.5% CI were estimated. Same methods were used for secondary criteria. For the main criteria a mixed model was built using treatment as fixed effect and center as random effect ; LSmeans were computed along with the 97.5% confidence interval. Since mixed model gave similar results than ANCOVA only the results from the variance analysis are displayed and discussed in this report.

Rates of patients achieving non-HDL-C target and LDL-C target levels were analyzed using a logistic model with center and treatment as explaining factors.

Safety analysis:

The number and frequency of patients experiencing a specific adverse event and the number of AEs were tabulated by group, system organ class, and prefered term.

Evolution of vital signs (weight, SBP, DBP and HR) was analyzed by ANOVA for repeated measurements.

Laboratory data were described at V3, V4, V5, V6 and V7, per group. For each parameter, change and percent change from baseline to W12 endpoint was provided for each group separately in each of the 2 strata. A Student's t-test for paired series was performed in order to test if the change observed between W12 endpoint and baseline was significantly different from 0 (= no change) in each treatment group. Moreover an analysis of covariance adjusted on baseline was performed to test the difference at W12 endpoint between treatment groups in each stratum.

Summary - Conclusions:

EFFICACY CONCLUSIONS

1301 patients were selected to participate in the study. 737 patients were considered as screening failures and 564 were randomized at W0. 291 belonged to the high CV risk stratum and 273 to the very high CV risk stratum. Randomization was well-balanced. In the high CV risk stratum, 146 patients were allocated to the Simvastatin group and 145 to the Fenofibrate/Pravastatin combination group. In the very high CV risk stratum, 136 patients were allocated to the Simvastatin + Ezetimibe group and 137 to the Fenofibrate/Pravastatin combination + Ezetimibe group. All but one patients took at least one unit of the study drug between W0 and W12 (N=563).

As 23 patients were withdrawn from the study during the efficacy phase and 4 patients were not treated between W12 and 24, 537 patients were therefore included in the analysis of the safety phase (281 were treated with the Fenofibrate/Pravastatin combination and 256 with the Fenofibrate/Pravastatin combination associated with Ezetimibe). Given that non-HDL-C endpoint could not be determined in 9 patients, the ITT analysis involved 555 patients.

Baseline characteristics and especially lipid levels were well matched between groups within each stratum. Compliance was very good during both phases of the study.

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Efficacy results are summarized below.

Stratum 1 : High CV risk patients

ITT - Stratum 1 - Mean percent change from baseline to W12 on all analyzed parameters for ITT analyzed set

	Simvastatin 20mg N=145		Fenofibrate/Pravastatin 160/40 mg N=144		Comparative p-value between treatments (Lsmeans) [97.5% one sided test CI]
Parameters	Relative delta (%) W12 endpoint-baseline	p-value for relative delta W12 endpoint-baseline	Relative delta (%) W12 endpoint-baseline	p-value for relative delta W12 endpoint-baseline	
Non-HDL cholesterol	**-7.03±20.22**	**<0.0001**	**-12.61±24.00**	**<0.0001**	**0.008]-∞;-1.13]**
LDL cholesterol	-6.86±21.69	0.0002	-5.25±25.71	0.016	0.295]-∞;6.63]
Triglycerides	**4.48±46.48**	**0.248**	**-28.07±41.91**	**<0.0001**	**<0.0001]-∞;- 23.35]**
HDL cholesterol	**1.92±15.03**	**0.127**	**6.23±16.43**	**<0.0001**	**0.008 [0.82;+∞[**
Total Cholesterol	-5.39±15.43	<0.0001	-8.55±18.41	<0.0001	0.035]-∞;0.27]
Apo A1	3.32±10.16	0.0001	3.46±13.21	0.002	0.366 [-2.19;+∞[
Apo B	-6.12±17.58	<0.0001	-8.62±24.43	<0.0001	0.098]-∞;1.61]
Apo B/Apo A1 ratio	-8.63±19.01	<0.0001	-9.91±28.45	<0.0001	0.248]-∞;3.60]
Fibrinogen	**-1.53±22.88**	**0.442**	**-9.68±17.73**	**<0.0001**	**<0.0001]-∞;-7.20]**
Hs CRP	-0.33 ± 6.72**	-	-0.35 ± 3.20**	-	-

** p values are to be compared to type 1 error risk set at 0.025 (one-sided test)*
*** absolute delta W12 endpoint-baseline (mg/L)*

The study demonstrated the more potent efficacy of the Fenofibrate 160 mg/Pravastatin 40 mg combination over Simvastatin 20 mg in decreasing the non-HDL-C level of patients at high CV risk. Indeed after twelve weeks of treatment, a significant decrease in non-HDL-C was observed in both treatment groups (-12.61±24.00 %, p<0.0001 for the Fenofibrate/Pravastatin 160/40 mg combination and -7.03±20.22 %, p<0.0001 for Simvastatin 20 mg) with a significant difference in favour of the Fenofibrate/Pravastatin combination (p=0.008). Fenofibrate 160 mg/Pravastatin 40 mg combination was also found to be more effective than Simvastatin 20 mg in reducing TG (p<0.0001) and fibrinogen (p<0.0001) levels and in increasing the HDL-C level (p=0.008).

No difference was found between groups neither on apolipoproteins A1 and B, total cholesterol nor on LDL-C levels.

In the high CV risk stratum, 42.36 % of patients achieved the non-HDL-C target level (<130 mg/dL) at the W12 endpoint in the Fenofibrate/Pravastatin group; this proportion was significantly greater than in the Simvastatin group (24.14 %, p=0.001). No difference was found in the proportion of patients having achieved the LDL-C target levels at the W12 endpoint (LDL-C<100 mg/dL). Combined non-HDL-C and LDL-C target level at W12 was achieved more frequently by patients treated with the Fenofibrate/Pravastatin combination (28.47 % versus 17.93 %, p=0.03).

Stratum 2 : Very high CV risk patients

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ITT - Stratum 2 - Mean percent change from baseline to W12 on all analyzed parameters for ITT analyzed set

Parameters	Simvastatin 20mg + Ezetimibe 10 mg N=133		Fenofibrate/Pravastatin 160/40 mg + Ezetimibe N=133		Comparative p-value between treatments (Lsmeans) [97.5% one sided test CI]
	Relative delta (%) W12 endpoint-baseline	p-value for relative delta W12 endpoint-baseline	Relative delta (%) W12 endpoint-baseline	p-value for relative delta W12 endpoint-baseline	
Non-HDL cholesterol	-24.97±21.36	<0.0001	-20.91±21.97	<0.0001	0.089]-∞; 8.82]
LDL cholesterol	-25.51±28.99	<0.0001	-19.44±23.92	<0.0001	0.050]-∞;11.65]
Triglycerides	**-8.70±68.04**	**0.143**	**-22.31±35.54**	**<0.0001**	**0.015]-∞; -1.48]**
HDL cholesterol	0.57±14.41	0.650	3.38±17.82	0.030	0.066 [-0.91 ;+∞[
Total Cholesterol	-19.39±16.84	<0.0001	-15.24±16.43	<0.0001	0.032]-∞; 7.76]
Apo A1	0.95±10.60	0.304	2.88±12.73	0.010	0.063 [-0.62;+∞[
Apo B	-18.38±18.77	<0.0001	-15.38±20.21	<0.0001	0.149]-∞;7.10]
Apo B/Apo A1 ratio	-19.00±17.82	<0.0001	-16.19±24.46	<0.0001	0.195]-∞; 7.40]
Fibrinogen	**0.67±17.42**	**0.667**	**-11.78±16.69**	**<0.0001**	**<0.0001]-∞; -8.48]**
Hs CRP	-1.12 ± 8.09**	-	-1.72 ± 5.71**	-	-

** p values are to be compared to type 1 error risk set at 0.025 (one-sided test)*
*** absolute delta W12 endpoint-baseline (mg/L)*

In the very high CV risk stratum, no difference was observed between the Fenofibrate 160 mg/Pravastatin 40 mg + Ezetimibe 10 mg and Simvastatin 20 mg + Ezetimibe 10 mg in reducing non-HDL-C level.

The Fenofibrate 160 mg/Pravastatin 40 mg combination + Ezetimibe 10 was found more effective than Simvastatin 20 mg + Ezetimibe 10 mg in reducing TG (p=0.015) and fibrinogen (p<0.0001) levels and a non-significant trend to improvement was observed on HDL-C level (p=0.066). No difference was found between the groups neither on total cholesterol , apolipoproteins A1 and B nor on LDL-C levels.

In the very high CV risk stratum, 42.11 % of patients achieved the non-HDL-C target level (<100 mg/dL) at the W12 endpoint in the Fenofibrate/Pravastatin + Ezetimibe group, a similar proportion than in the Simvastatin + Ezetimibe group (40.60 %, p=0.803); no difference was found neither in the proportion of patients having achieved the LDL-C target levels at W12 (LDL-C<70 mg/dL) nor in the proportion of patients having achieved the combined non-HDL-C and LDL-C target levels.

SAFETY CONCLUSIONS

Duration of each period and mean cumulative received dose of study drugs were in conformity with the protocol requirements. During the 12-week blinded period, 86 patients reported at least one AE. Any relevant difference was found in frequency of AEs neither between strata nor between groups within stratum. AEs were mainly of mild to moderate intensity. AEs were unfrequent and unspecific. The percentage of patients with at least one emergent adverse event was similar between treatments

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(from 14.07 % in the Simvastatin + Ezetimibe group to 15.86 % in the Fenofibrate/Pravastatin group). The number of patients presenting at least one related adverse events ranked from 2.96 % for Simvastatin + Ezetimibe to 6.57 % for Fenofibrate/Pravastatin + Ezetimibe. The percentage of patients presenting at least one AE related to the study drug that led to patient's withdrawal was also similar between treatments (from 0.69 % for the Fenofibrate/Pravastatin combination to 2.92 % for Fenofibrate/Pravastatin + Ezetimibe).

Six patients reported a total of 7 SAEs. Only one patient reported a SAE possibly related to drug to drug interaction. This patient from the very high CV risk stratum received concomitantly acenocoumarol following an aortic valvuloplasty and experienced a dramatic increase in INR (International normalized ratio) with gastrointestinal haemorrhage and subsequent anaemia.

No new adverse events related to test treatment were observed and no synergistic safety problems appeared even with the triple combination Fenofibrate/Pravastatin 160/40 mg + Ezetimibe 10 mg.

During the blinded W0-W12 period, there was a similar increase in CPK levels in all groups. Elevations in CPK levels within the 3-5 ULN range were reported for 10 patients: 7 from the high CV risk stratum (6 treated with the Fenofibrate/Pravastatin combination and 1 treated with Simvastatin) and 3 in the very high CV risk stratum (1 treated with Fenofibrate/Pravastatin + Ezetimibe and 2 treated with Simvastatin + Ezetimibe). None of these patients reported any muscular symptoms. Furthermore, there was no patient with CPK levels > 5 ULN. ASAT levels increased of 9.58±39.00 % in the Fenofibrate/Pravastatin group and remained unchanged in the Simvastatin group in the high CV risk stratum. ALAT levels reached > 3 ULN in 2 patients from the very high CV risk stratum (1 from each treatment group). Elevations in CPK levels and elevations in ALAT and ASAT levels were constantly transient, quickly resolved, isolated and never led to study discontinuation. There was a more important increase in blood creatininemia in the groups receiving the Fenofibrate/Pravastatin combination or Fenofibrate/Pravastatin combination + Ezetimibe. Any relevant changes were found neither in fasting blood glucose nor in HbA1c. Total bilirubin levels remained unchanged and alkaline phosphatase levels significantly decreased in the Fenofibrate/Pravastatin combination group and in the Fenofibrate/Pravastatin combination + Ezetimibe group. Homocysteine levels significantly increased in the Fenofibrate/Pravastatin combination group and in the Fenofibrate/Pravastatin combination + Ezetimibe group.

Similar results were found during the W12 - W24 period when all patients were receiving Fenofibrate/Pravastatin combination associated or not with Ezetimibe.

So both clinical and laboratory results showed the good safety of the Fenofibrate 160 mg/Pravastatin 40 mg combination. Especially no myopathy, rhabdomyolysis or even significant muscular symptoms were reported even in patients with moderate elevation in CPK levels.