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CLINICAL STUDY REPORT SUMMARY

SPONSOR	:	Laboratoires SMB S.A.
ADDRESS	:	Rue de la Pastorale, 26-28 B-1080 Bruxelles BELGIUM ☏: +32.2.411.48.28 🖷: +32.2.411.28.28
INVESTIGATIONAL PRODUCT	:	Fenofibrate 160 mg – Pravastatin 40 mg
STUDY CODE	:	FENOPRA-III-05-1
TITLE	:	An open-label phase III study to evaluate the safety of the combination (Fenofibrate/Pravastatin 160-40 mg) during 24 weeks, in high vascular risk patients with combined hyperlipidemia.
STUDY INITIATION	:	First patient included: January 23, 2006
STUDY TERMINATION	:	Last patient completed: June 5, 2007
INDICATION	:	Lipid lowering agent
CLINICAL PHASE	:	Phase III: Safety study
SPONSOR'S OFFICER	:	Dr. Monte Coffiner, M.D.
CONTACT DETAILS	:	Rue de la Pastorale, 26-28 B-1080 Brussels BELGIUM ☏: +32.2.411.48.28 🖷: +32.2.411.28.28
CO-ORDINATING INVESTIGATOR	:	Pr. Gérald Luc CHRU Lille – Hôpital Claude Huriez Service médecine interne A 1 place Verdun 59037 Lille Cedex FRANCE
RESEARCH ORGANISATION	:	ICTA PM 11 rue du Bocage 21121 Fontaine-les-Dijon FRANCE ☏: +33.3.80.53.40.00 🖷: +33.3.80.57.10.22 PHARMNET Pekova 13 18600 Prague 8 CZECH REPUBLIC ☏: +420.2.248.13166 🖷: +420.2.248.13204
GCP STATEMENT	:	The study described within this report was conducted in accordance with Good Clinical Practices (GCP) and International Conference of Harmonization (ICH) (including the archiving of essential documents).
VERSION/DATE	:	Final version dated January 20, 2009

2. SYNOPSIS

Name of Sponsor: **Laboratoires SMB S.A.** Name of Finished Product: **Not yet determined** Name of Active Ingredient: **Fenofibrate/Pravastatin 160-40 mg**	Individual Study Table Referring to Module 5 of the dossier Volume: Page:	(For National Authority Use Only)

Title of the study:	An open-label phase III study to evaluate the safety of the combination (Fenofibrate/Pravastatin 160-40 mg) during 24 weeks, in high vascular risk patients with combined hyperlipidemia.
Coordinating Investigator:	Pr Gérald Luc, CHRU de Lille - Hôpital Claude Huriez, Service médecine interne A, 1, place Verdun, 59037 Lille cedex, France
Study Centre:	56 active centres: 38 in France and 18 in Czech Republic
Studied Period:	From January 23, 2006 (first inclusion) to June 5, 2007 (last follow-up visit)
Phase of development:	Phase III (Safety study)
Objective:	To evaluate the safety of the combination Fenofibrate/Pravastatin 160-40 mg in high vascular risk patients as defined in the NCEP ATP III with combined hyperlipidemia.
Methodology:	Multicentre, open-label 24 week phase III safety study.
Number of patients:	344 patients were included 296 patients completed the study. *Safety analysis*: 342 patients *Efficacy analyses*: ITT: 307 patients Per Protocol: 266 patients
Diagnosis and main criteria for inclusion:	- Male and female, aged 18 years and older - High vascular risk patients according to the NCEP ATP III: ▪ high vascular risk patients with coronary heart disease (CHD) or other clinical forms of atherosclerotic disease or diabetes or multiple risk factors that confer a 10 year CHD risk > 20%; ▪ or very high vascular risk patients with cardiovascular disease (CVD): CHD or other clinical forms of atherosclerotic disease and multiple major risk factors (especially diabetes) or severe and poorly controlled risk factors (especially smoking) or multiple risk factors of the metabolic syndrome - Documented combined hyperlipidemia - Taking a statin therapy for at least 8 weeks at the selection visit - Non-HDLc ≥ 130/md/dl (≥ 3.36 mmol/L) if high absolute risk, or non-HDLc ≥ 100/md/dl (≥ 2.58 mmol/L) if very high absolute risk at the selection visit - TG ≥ 100 mg/dl and ≤ 500 mg/dl (≥ 1.71 mmol/L and ≤ 5.71 mmol/L)
Test Product:	Fenofibrate/Pravastatin 160-40 mg, one capsule, taken once a day orally, containing 160 mg of Fenofibrate and 40 mg of Pravastatin (batch number GF05-032).
Reference Therapy:	None

Duration of treatment:	*Selection period*: 2 weeks as a maximum during which the patients were under their usual statin therapy for at least 8 weeks. *Safety period*: open-label 24 week period during which the patients took the study treatment (Fenofibrate/Pravastatin 160-40 mg).

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Criteria for evaluation:	**Safety (primary criteria)** Adverse events, laboratory data, physical examination, incidence of myopathy and/or rhabdomyolysis, increase of transaminase levels (ASTA/ALAT) (threefold the upper normal limit - UNL), increase of CPK levels (fivefold the upper normal limit), increase of creatinemia (> 20 mg/l or > 177 µmol/l) and decrease of creatinine clearance (< 50 ml/min), vital signs, ECG, and withdrawal or drop-out rate. **Efficacy (secondary criteria)** **Primary endpoint:** The mean percent change in non-HDL cholesterol levels at the end of the study (laboratory evaluation B5/W24) compared to the baseline value (value recorded at the B1 laboratory exam). **Secondary endpoints:** The mean percent changes from baseline in other biological parameters levels at the end of the study (LDLc, HDLc, triglycerides, total cholesterol, $ApoA_1$, ApoB, ratio ApoB/$ApoA_1$, fibrinogen and HsCRP), the proportion of patients achieving the therapeutic goals defined by NCEP ATP III at the end of the study, and the mean percent change in estimated 10 year cardiovascular risk for myocardial infarction (PROCAM risk calculator) at the end of the study compared to the estimated cardiovascular risk at baseline.
Study procedures:	There was a selection period of 2 weeks maximum (0 to 14 days) prior to the inclusion (all the patients had to be under their usual statin therapy for at least 8 weeks) during which the baseline data were collected. Patients then entered in an open-label, study period of the combination Fenofibrate/Pravastatin 160-40 mg for a duration of 24 weeks. Five visits were scheduled during the whole study period.
Statistical analysis:	**Software**: All data were analysed using the software SAS® System Windows® based version 8.2. **Significance level**: All statistical tests were two-tailed and the level of significance was set at 0.05. **Statistical analysis:** Absolute values and mean percent changes from baseline (B1 laboratory exam) in the efficacy endpoints (non-HDLc, LDLc, HDLc, triglycerides, total cholesterol, $ApoA_1$, ApoB, ratio ApoB/$ApoA_1$, fibrinogen, HsCRP and estimated 10 year-CHD risk) were summarised at each time point by means of descriptive statistics during the study period. 95% confidence intervals (CI) were presented for the mean assuming a normal distribution. Comparisons were made between the baseline and each time point by means of paired t-tests (or non-parametric tests if necessary). The proportions of patients achieving the therapeutic goals defined by NCEP ATP III were summarised at each time point by means of descriptive statistics only (percentages and 95% CI). All safety parameters were summarised by means of descriptive statistics during the study period.
Summary and Conclusions	

Study population:	482 patients were screened based on established inclusion and exclusion criteria at visit of selection (VS). At baseline (Week 0), 344 patients were included in the 24-week study period of the combination Fenofibrate/Pravastatin 160-40 mg. Two patients out of the 344 were excluded from the safety population as they did not take at least one dose of the active study medication after inclusion resulting in a safety population of 342 patients. Thirty-five (35) patients were excluded from the ITT population as they did not achieve at least one laboratory evaluation for lipid profile after inclusion resulting in an ITT population of 307 patients. Protocol violations and/or study withdrawals were reported during the study period for 41 patients, resulting in a Per Protocol (PP) population of 266 patients. Compliance over the whole study was 97.6%.

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Summary and Conclusions (continued)

Safety results:	
	The safety profile of the fixed-dose combination of Fenofibrate-Pravastatin evaluated with respect to the incidence of AEs and laboratory values was acceptable during the 24-week study period. During this period, one-hundred and thirty-seven patients (40.1%) experienced 253 treatment emergent adverse events (TEAEs), of which 50 (19.9%) were related to Fenofibrate/Pravastatin 160-40 mg. Thirty-one patients (9.1%) were withdrawn from the study because of an AE. Creatinine clearance decreased associated with blood creatinine increased (3,2%), diabetes mellitus (2,9%) and back pain (2,6%) were the most frequent AEs. Constipation (1,5%) and myalgia (1,5%) were the most frequent AEs related to the treatment. Seven patients (2.0%) had an elevation of ASAT and/or ALAT > 3 UNL. Five patients (1.5%) had an elevation of CPK > 3 UNL but <10 UNL. Twenty patients (5.8%) experienced 24 serious adverse events (SAEs) during the study period. None of them were related to the study drug (Fenofibrate/Pravastatin 160-40 mg). No death was observed during the study. Neither myopathy nor rhabdomyolysis were reported during the study. Vital signs (SBP, DBP and heart rate), physical examination and ECG results remained stable during the study.
Efficacy results:	
	The efficacy of the fixed dose combination Fenofibrate/Pravastatin 160-40 mg versus baseline (obtained after at least 8 weeks statin therapy) was demonstrated over the 24-week study period for non-HDLc, LDLc, HDLc, triglyceride, total cholesterol, $ApoA_1$, ApoB, ratio ApoB/$ApoA_1$, fibrinogen levels, and 10 year CHD risk. All these parameters were already significantly improved after 12 weeks of treatment. The HsCRP was the only parameter for which the significant improvement obtained after 6 weeks ($p=0.014$) and after 12 weeks ($p<0.001$) of treatment was not maintained after 24 weeks. The percentage of patients achieving the therapeutic goals according to the NCEP ATP III was 18.6% after 12 weeks and 19.9% at the end of the 24-week study period.
Conclusions:	During this 24-week study, the Fenofibrate/Pravastatin fixed dose combination (160-40 mg per day) was well tolerated by the 342 patients included and no particular safety concern was raised. The adverse event profile of the investigational product was as expected for a combination of fenofibrate and pravastatin, based on what is described for each monotherapy. No new adverse event was identified for the combination product versus existing monotherapy with fenofibrate and pravastatin.

	A significant improvement of the lipid profile and 10 year CHD risk was obtained after 12 weeks and 24 weeks of treatment with the Fenofibrate/Pravastatin 160-40 mg fixed dose combination in high and very high risk patients with combined hyperlipidemia..
Date of report:	January 20, 2009, Final version