SYNOPSIS

Name of Sponsor:
FOURNIER LABORATORIES IRELAND Ltd

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
SLV285

Name of Active Ingredient:
Fenofibrate/Simvastatin

Study Title:

A multicenter, double-blind, randomized study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 40 mg simvastatin alone.

Investigator(s):

63 investigators participated in this study.

Study Center(s):

Subjects were included in 22 centers in Australia, 7 centers in Estonia, 10 centers in Hungary, 7 centers in Latvia, 8 centers in Lithuania, and 9 centers in New Zealand.

Publication (Reference): Not Applicable

Study Period:

01 MAR 2006 (first subject first visit) to
26 AUG 2008 (last subject last visit)

Phase of Development: III

Objectives:

The primary objective was to evaluate after 12 weeks of treatment the efficacy of adding 145 mg fenofibrate to ongoing 40 mg simvastatin therapy to reduce TG and LDL-C and increase HDL-C, in subjects with mixed dyslipidemia (type IIb) at risk of cardiovascular disease not adequately controlled by 40 mg simvastatin alone.

The secondary objectives were: (1) to evaluate the efficacy of adding 145 mg fenofibrate to 40 mg simvastatin compared to 40 mg simvastatin monotherapy after 24 weeks of treatment on TG, HDL-C and LDL-C, (2) to evaluate the efficacy of adding 145 mg fenofibrate to 40 mg simvastatin compared to 40 mg simvastatin monotherapy after 12 and 24 weeks of treatment on non-HDL-C, TC, ApoAI, ApoB, ApoB/ApoAI ratio, high-sensitivity C-reactive protein (hsCRP), and fibrinogen, (3) to compare the safety of adding 145 mg fenofibrate to 40 mg simvastatin monotherapy with 40 mg of simvastatin over 24 weeks of treatment.

Methodology:

This was a multicenter, phase III, randomized, double-blind, 2-parallel arms, and comparative study with a 6-week simvastatin run-in period. Four hundred (400) subjects at risk of cardiovascular disease with mixed (type IIb) dyslipidemia, as documented in their medical file, were to be randomized.

The clinical study consisted of 2 phases: (1) a 6-week (+/- 1 week) run-in period with stable dose of 40 mg simvastatin, (2) a 24-week (+/- 2 weeks) blinded treatment period during which the subjects were treated with either 145 mg fenofibrate + 40 mg

simvastatin (feno145+simva40) or 145 mg fenofibrate placebo + 40 mg simvastatin (simva40). Treatments were to be taken in the evening with or without a meal: 1 tablet during the run-in and 2 tablets together during the double-blind period.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned: 400, Consented: 1390. Treated in run-in: 1187.

Randomized: 450 (stratification by gender and cardiovascular risk category).

Treated in double-blind: 449.

Analyzed:

Safety subject sample: 225 in the feno145+simva40 group and 224 in the simva40 group.

Full Analysis (FA) subject sample: 221 in the feno145+simva40 group and 219 in the simva40 group.

Per Protocol (PP) subject sample: 195 in the feno145+simva40 group and 198 in the simva40 group.

Diagnosis and Main Criteria for Inclusion:
Main criteria for inclusion

Subjects were to have: (1) CHD or CHD-risk equivalent per NCEP-ATP III (excluding diabetes) in whom 10-year risk for CHD was > 20% or with no CHD but multiple (2+) risk factors, (2) mixed (type IIb) dyslipidemia documented in the medical file.

Lipid randomization criteria

(1) if CHD or CHD-risk equivalent per NCEP-ATP III with 10-year risk for CHD > 20%: LDL-C ≥ 2.58 mmol/L (≥ 100 mg/dL) but < 4.91 mmol/L (< 190 mg/dL) or non-HDL-C ≥ 3.36 mmol/L (≥ 130 mg/dL) but < 5.69 mmol/L (< 220 mg/dL).

(2) if multiple (2+) risk factors with 10-year risk for CHD between 10 and 20%: LDL-C ≥ 3.36 mmol/L (≥ 130 mg/dL) but < 5.69 mmol/L (< 220 mg/dL) or non-HDL-C ≥ 4.13 mmol/L (≥ 160 mg/dL) but < 6.46 mmol/L (< 250 mg/dL).

Test Product, Dose and Mode of Administration, Batch Number:

Coadministered fenofibrate + simvastatin, Dose: fenofibrate: 145 mg/day, simvastatin: 40 mg/day, Oral, Clinical batch Nos.: 333/20, 333/21, 333/22, 333/23, 333/24, 333/25.

Duration of Treatment: 6-week run-in period, 24 weeks in the double-blind period.

Run-in and Reference Therapy, Dose and Mode of Administration, Batch Number:

Simvastatin (Zocor®, MSD), Dose: 40 mg, Oral, Clinical batch: run-in: Nos.: 333/10, 333/11, 333/12, double-blind period: 333/20, 333/21, 333/22, 333/23, 333/24, 333/25.

Criteria for Evaluation

Efficacy:

The primary efficacy variables were the percent change from baseline to 12 weeks of treatment in TG, HDL-C and LDL-C. The secondary efficacy variables were: (1) the percent change from baseline to 24 weeks of treatment in TG, HDL-C and LDL-C, (2) the percent change from baseline to 12 weeks and 24 weeks of treatment in non-HDL-C, TC, LDL size (12 weeks only), ApoAI, ApoB and ApoB/ApoAI ratio, (3) the change from baseline to 12 weeks and 24 weeks in hsCRP and fibrinogen, (4) the percentage of subjects reaching the NCEP-ATP III targets after 12 weeks and 24 weeks for LDL-C, TG, non-HDL-C, LDL-C and TG, non-HDL-C and TG, (LDL-C or non-HDL-C) and TG levels.

Safety:

Adverse events (AEs), biochemistry: creatine kinase (CK), aspartate aminotransferase (AST), alanine amino transferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, serum creatinine, total bilirubin, hematology: white blood (WBC) and differential count, red blood cells (RBC), hemoglobin, hematocrit and platelets.

Statistical Methods:

Efficacy

The distribution of each efficacy variable was tested for normality, by means of Quantile-Quantile plot and plots of residuals. In case of the data being not normally distributed, a logarithmic transformation of the data was to be performed.

The primary analysis, on the FA subject sample, consisted in testing the superiority of feno145+simva40 over simva40 on percent change in TG, LDL-C and HDL-C from baseline to 12 weeks of treatment. An analysis of covariance (ANCOVA) model (if no violation of the usual assumptions) was used for each criterion and the corresponding 95% confidence interval (CI) of the difference between the two treatment groups was calculated. The level of statistical significance was 5% two-sided. The superiority of feno145+simva40 was demonstrated for the 3 parameters if the 95% CI limits were on the negative side for TG and LDL-C, and on the positive side for HDL-C (p values for treatment effect < 0.05). The covariates were: baseline value at end of simvastatin run-in, gender, cardiovascular risk category. The ANCOVA was repeated on the PP subject sample.

A sensitivity analysis was performed to assess whether any other covariates or interaction terms contributed in a systematic way to the variability observed in the responses: country, treatment group and gender interaction, treatment group and cardiovascular risk category interaction, treatment group and country interaction. This sensitivity analysis was performed on the FA subject sample.

The main secondary efficacy analysis, on the FA subject sample, consisted in testing the superiority of feno145+simva40 over simva40 on percent change in TG, LDL-C and HDL-C from baseline to 24 weeks of treatment. The same ANCOVA model and the same sensitivity analysis as for the primary analysis were used.

Other secondary efficacy analyses on FA subject sample and PP subject sample (12 weeks only) consisted in comparing feno145+simva40 with simva40 on: (1) percent change from baseline to 12 weeks and from baseline to 24 weeks in TC, non-HDL-C, LDL size (12 weeks only), ApoAI, ApoB and ApoB/ApoAI, (2) absolute change from baseline to 12 weeks and from baseline to 24 weeks in hsCRP and fibrinogen, (3) NCEP-ATP III targets for LDL-C, TG, non-HDL-C, LDL-C and TG, non-HDL-C and TG, (LDL-C or non-HDL-C) and TG at 12 weeks and at 24 weeks of treatment. For lipids and inflammatory parameters, the same ANCOVA model as for the primary analysis was used. For the NCEP-ATP III targets, a logistic regression model was used and the odds ratio and associated 95% CI were calculated.

Descriptive statistics were provided by treatment group and by subgroup: gender, cardiovascular risk category (high-risk: CHD or CHD equivalents [10-year risk > 20%] and moderately high-risk: multiple (2+) risk factors [10-year risk 10 to 20%], age category (< 65 years and ≥ 65 years), TG and LDL-C class: high TG (≥ 2.28 mmol/L)/high LDL-C (≥ 3.36 mmol/L), high TG/low LDL-C (< 3.36 mmol/L), low TG (< 2.28 mmol/L)/high LDL-C, low TG/low LDL-C, and country.

Safety

The analysis of AEs included: (1) the incidence of AEs reported in the run-in period: all AEs, serious AEs (SAEs), AEs leading to premature discontinuation, (2) the incidence of treatment-emergent AEs (TEAEs) reported between baseline and 12 weeks, between 12 and 24 weeks and between baseline and 24 weeks on the Safety sample: all TEAEs, TEAEs related to study treatment, TESAEs, TEAEs leading to premature discontinuation, TEAEs with incidence ≥ 2% in any treatment group, TEAEs of interest (increase in liver enzymes, total bilirubin and CK, and musculoskeletal and connective tissue disorders). TEAEs were also analyzed by subgroup: age, gender, cardiovascular risk, and country.

The analysis of laboratory safety tests included descriptive statistics and change from baseline to 12 and 24 weeks, classification according to reference range, shift tables indicating the change in abnormal category, from baseline to 12 weeks, 12 weeks to 24 weeks and baseline to 24 weeks.

The analysis of vital signs included summary statistics and change from baseline to 6, 12 and 24 weeks, and the incidence per treatment group of marked abnormalities.

Summary - Conclusions

Efficacy Results:

The results of the primary efficacy analysis are presented in Table A.

Table A: TG, LDL-C and HDL-C at Baseline, 12 Weeks, Percent Change at 12 Weeks from Baseline and Treatment Comparison – FA Subject Sample

	Feno145 + Simva 40 (n = 221)			Simva 40 (n = 219)			Treatment Comparison (%) [c]	p
	Base.[a]	12 Wk	Change [b]	Base.[a]	12 Wk	Change [b]		
TG (mmol/L) [d]	2.61	1.70	-35.1%	2.57	2.41	-9.6%	-28.2 (-32.9, -23.1)	<0.001
LDL-C (mmol/L) [e]								
All	3.28	3.00	-7.7%	3.30	3.07	-6.5%	-1.2 (-5.2, 2.7)	0.539
Females [e, f]	3.46	2.87	-12.3%	3.50	3.21	-3.2%	-9.1 (-16.0, -2.2)	0.010
Males [e, g]	3.19	3.07	-2.6%	3.21	3.01	-5.8%	3.2 (-1.4, 7.9)	0.173
HDL-C (mmol/L) [e]	1.22	1.28	7.3%	1.21	1.19	0.8%	6.5 (3.8, 9.1)	<0.001

a. Baseline, b. LS-mean of percent change, c. (Feno 145 + Simva 40) – Simva 40, difference in percent change and 95% CI, d. Medians at baseline and at 12 weeks and ANCOVA done on Log-transformed data, e. Means at baseline and at 12 weeks. f. n = 70 in the feno145+simva40 group and n = 68 in the simva group, g. n = 151 in the 2 groups. A Log transformation was applied for TG; the tabulated LS-means by group are obtained via back-transformation of their model-based counterparts using the formulas (exp(LSmeans) − 1) x 100 and for treatment comparison using (exp(LSmeans difference) − 1) x 100. This explains why the treatment effect differs from the difference between individual treatment effects.

After 12 weeks of treatment, in subjects previously treated with 40 mg simvastatin for 6 weeks, feno145+simva40 was superior to simva40 in reducing TG and in increasing HDL-C. The sensitivity analysis on percent changes in LDL-C showed a statistically significant interaction between gender and treatment (p = 0.004) that did not permit to conclude on the superiority of feno145+simva40 on LDL-C overall. Feno145+simva40

was superior to simva40 in reducing LDL-C in female subjects, but not in male subjects. The PP analysis showed similar results.

The results of the key secondary efficacy variables are presented in Table B.

Table B: TG, LDL-C and HDL-C at Baseline, 24 Weeks, Percent Change at 24 Weeks from Baseline and Treatment Comparison – FA Subject Sample

	Feno145 + Simva 40 (n = 213)			Simva 40 (n = 203)			Treatment Comparison (%) [c]	p
	Base.[a]	24 Wk	Change [b]	Base.[a]	24 Wk	Change [b]		
TG (mmol/L)[d]	2.61	1.76	-31.8%	2.54	2.56	-5.9%	-27.6 (-32.9, -21.8)	<0.001
LDL-C (mmol/L) [e]								
All	3.27	3.08	-4.8%	3.30	3.34	2.4%	-7.2 (-12.2, -2.2)	0.005
Females [e, f]	3.47	2.94	-11.0%	3.49	3.62	9.3%	-20.4 (-29.1, -11.6)	<0.001
Males [e, g]	3.19	3.15	0.2%	3.22	3.21	0.8%	-0.6 (-6.4, 5.3)	0.846
HDL-C (mmol/L) [e]	1.22	1.28	5.4%	1.22	1.22	0.7%	4.6 (1.9, 7.4)	0.001

a. Baseline, b. LS-mean of percent change, c. (Feno 145 + Simva 40) – Simva 40, difference in percent change and 95% CI, d. Medians at baseline and at 24 weeks and ANCOVA done on Log-transformed data, e. Means at baseline and at 24 weeks. f. n = 67 in the feno145+simva40 group and n = 61 in the simva group, g. n = 146 in the feno145+simva40 group and n = 142 in the simva group. A Log transformation was applied for TG; the tabulated LS-means by group are obtained via back-transformation of their model-based counterparts using the formulas (exp(LSmeans) − 1) x 100 and for treatment comparison using (exp(LSmeans difference) − 1) x 100. This explains why the treatment effect differs from the difference between individual treatment effects..

After 24 weeks of treatment, the superiority of feno145+simva40 over simva40 in reducing TG and in increasing HDL-C was maintained, with differences between groups close to those observed after 12 weeks of treatment. Regarding LDL-C, a statistically significant interaction between gender and treatment was found at 24 weeks ($p < 0.001$) as at 12 weeks. Feno145+simva40 was superior to simva40 in female subjects only.

The results of the analysis of other secondary variables after 12 weeks of treatment are presented in Table C.

Table C: Non-HDL-C, LDL size, ApoB and ApoB/ApoAI at Baseline, 12 Weeks, Percent Change at 12 Weeks from Baseline and Treatment Comparison – FA Subject Sample

	Feno145 + Simva 40 (n = 221)			Simva 40 (n = 219)			Treatment Comparison (%) [c]	p
	Base.[a]	12 Wk	Change [b]	Base.[a]	12 Wk	Change [b]		
Non-HDL-C (mmol/L)	4.28	3.82	-11.3%	4.32	4.15	-4.3%	-7.0 (-10.7, -3.2)	<0.001
LDL size (Å) [d]	231.8	235.2	1.6%	232.1	232.1	0.2%	1.3 (0.9, 1.8)	<0.001
ApoB (g/L) [e]	1.00	0.93	-5.7%	1.00	0.99	-0.2%	-5.5 (-9.0, -2.0)	0.002
ApoB/ApoAI [e]	0.74	0.68	-8.4%	0.75	0.74	-0.1%	-8.3 (-12.5, -4.0)	<0.001

Means at baseline and at 12 weeks. a. Baseline, b. LS-mean of percent change, c. (Feno 145 + Simva 40) – Simva 40, difference in percent change and 95% CI, d. n = 101 in the feno145+simva40 group and 98 in the simva40 group, e. n = 211 in the feno145+simva40 group and 209 in the simva40 group.

After 12 weeks of treatment, in subjects previously treated with 40 mg simvastatin for 6 weeks, feno145+simva40 was superior to simva40 in reducing non-HDL-C, ApoB, ApoB/ApoAI ratio, and in increasing LDL size.

The results of the analysis of other secondary variables after 24 weeks of treatment are presented in Table D.

Table D: Non-HDL-C, ApoB and ApoB/ApoAI at Baseline, 24 Weeks, Percent Change at 24 Weeks from Baseline and Treatment Comparison – FA Subject Sample

	Feno145 + Simva 40 (n = 213)			Simva 40 (n = 203)			Treatment Comparison (%) [c]	p
	Base.[a]	24 Wk	Change [b]	Base.[a]	24 Wk	Change [b]		
Non-HDL-C (mmol/L)	4.28	3.90	-8.6%	4.31	4.35	1.7%	-10.3 (-14.9, -5.7)	<0.001
ApoB (g/L) [d]	0.99	0.95	-3.4%	1.00	1.04	5.9%	-9.3 (-13.7, -4.8)	<0.001
ApoB/ApoAI [d]	0.73	0.69	-6.2%	0.75	0.75	2.1%	-8.3 (-15.2, -1.4)	0.019

Means at baseline and at 24 weeks. a. Baseline, b. LS-mean of percent change, c. (Feno145 + Simva 40) – Simva 40, difference in percent change and 95% CI, d. n = 204 in the feno145+simva40 group and 194 in the simva40 group.

After 24 weeks of treatment, feno145+simva40 was superior to simva40 in reducing non-HDL-C, ApoB, and ApoB/ApoAI ratio.

NCEP-ATP III targets

At both 12 weeks and 24 weeks, there were significantly more subjects at target for TG, non-HDL-C, LDL-C and TG, non-HDL-C and TG, and (LDL-C or non-HDL-C) and TG in the feno145+simva40 group than in the simva40 group. For TG, the odds ratio was 4.16 at 12 weeks and 4.52 at 24 weeks. For non-HDL-C, LDL-C and TG, non-HDL-C and TG, and (LDL-C or non-HDL-C) and TG, the odds ratios varied between 1.89 and 3.09 at 12 weeks and between 2.58 and 5.74 at 24 weeks.

For LDL-C only, the odds ratio was 1.17 at 12 weeks and 1.54 at 24 weeks (not statistically significant).

Safety Results:

During the 6-week run-in period, with all the subjects (n = 1187) on 40 mg simvastatin, 323 (27.2%) subjects experienced at least 1 AE. The main safety findings were abnormal laboratory investigations, mainly increased GGT (5.5%), increased blood glucose (3.3%), and increased serum creatinine levels (2.8%). The incidence of increased transaminases and CK was between 0.3 and 0.8%, that of myalgia, musculoskeletal pain, muscle spams, and muscular weakness was between 0.1 and 0.4%. Gastrointestinal disorders were reported in 2.7% of the subjects. Fifteen (1.3%) subjects reported at least 1 SAE during the run-in period, and 74 (6.2%) subjects discontinued the study because of AEs.

During the double-blind treatment period 2 deaths were reported. One subject in the feno145+simva40 group died in a road traffic accident. One subject in the simva40 group died from acute coronary syndrome, which was considered as not related to study treatment.

TESAEs were reported in 5 (2.2%) subjects in the feno145+simva40 group and 10 (4.5%) subjects in the simva40 group between baseline and 12 weeks and in 7 subjects in each group between 12 and 24 weeks. Two TESAEs were considered to be related to study treatment: hepatic steatosis with persisting transaminases elevation in a subject in the feno145+simva40 group and increased transaminases in a subject in the simva40 group.

Four (1.8%) subjects in the feno145+simva40 group and 7 (3.1%) subjects in the simva40 group prematurely discontinued the study between baseline and 12 weeks because of AEs. Among these subjects, 5 subjects prematurely discontinued because of myalgia: 2 subjects in the feno145+simva40 group and 3 subjects in the simva40 group. Three subjects prematurely discontinued between 12 and 24 weeks: the 2 subjects who died (see above) and 1 subject in the simva40 group who had increased transaminases.

Overall, 5 (2.2%) subjects in the feno145+simva40 group and 9 (4.0%) subjects in the simva40 group withdrew prematurely for AEs.

The most common TEAEs reported during the double-blind treatment period in either treatment group were for abnormal laboratory investigations: 21.3% in the feno145+simva40 group and 20.1% in the simva40 group.

Increase in creatinine was the most frequent laboratory abnormality. Increases in creatinine > 30 µmol/L from baseline were found in 17.0% of the subjects in the feno145+simva40 group and in 13.5% in the simva40 group. The mean change from baseline to 24 weeks was 13.2 µmol/L in the feno145+simva40 group and 5.0 µmol/L in the simva40 group.

AEs of special interest (increase in liver enzymes and musculoskeletal symptoms) were rare and showed no differences between treatment groups.

The incidence of TEAEs for increases in ALT/AST (> 3 x ULN), total bilirubin (> 1.5 x ULN) or CK (> 5 x ULN) was between 0.4 to 1.8%, with no differences between the treatment groups. Increases in bilirubin were reported in 5 (2.3%) subjects in the simva40 group, in none of the subjects in the feno145+simva40 group.

Myalgia was reported with the same frequency with the 2 treatments: 3.6% of the subjects. Other musculoskeletal and connective tissue disorders (pain in extremity, muscle spasms, fibromyalgia, musculoskeletal pain, and musculoskeletal chest pain) were rare (0.9% or less) and reported with the 2 treatments.

Gastrointestinal disorders were reported in 14 (6.2%) subjects in the feno145+simva40 group and in 15 (6.7%) subjects in the simva40 group.

One subject treated in the feno145+simva40 group experienced deep vein thrombosis.

Conclusion:

This double-blind, 24-week, parallel-group study conducted in subjects with mixed dyslipidemia (type IIb) at risk of CVD not adequately controlled by 40 mg simvastatin monotherapy showed that feno145+simva40 was superior to simva40 in reducing TG and in increasing HDL-C after both 12 weeks (primary endpoint) and 24 weeks of treatment. Regarding LDL-C, feno145+simva40 was superior to simva40 at 12 and 24 weeks in female subjects only. Feno145+simva40 and simva40 were well tolerated.