SYNOPSIS

Title of the study: A randomized, double blind, placebo controlled study evaluating the glycemic effect of rimonabant added to metformin in patients with type 2 diabetes insufficiently controlled with metformin monotherapy (EFC10518)			
Investigators: No Principal Investigator was planned or identified for this study			
Study centers: The study was conducted at 101 centers in 13 countries (Indonesia, Lithuania, Malaysia, Mexico, Philippines, Poland, Romania, Russia, Slovakia, Taiwan, Thailand, Ukraine, and the United States of America)			
Publications (reference): None			
Study period: Date first patient enrolled: 28 May 2008 Date last patient completed: 18 February 2009			
Phase of development: Phase 3b			
Objectives: The objectives of the protocol were as follows: ***Primary***: To demonstrate the superiority of rimonabant 20 mg versus placebo when added daily to metformin 1500 mg/day (or more) on glycemic control (glycosylated hemoglobin A_{1c} [HbA_{1c}]) after 36 weeks treatment in patients with type 2 diabetes mellitus. ***Secondary***: To evaluate the: • effect of rimonabant 20 mg added to metformin over a period of 36 weeks on: additional markers of glycemic control (eg, fasting plasma glucose, homeostasis model of insulin resistance, insulin); lipid profile (high-density lipoprotein cholesterol (HDL-C), triglycerides, low-density lipoprotein cholesterol (LDL-C), total cholesterol, total cholesterol/HDL-C); body weight; abdominal obesity (as measured by waist circumference). • safety of rimonabant 20 mg added to metformin during the entire study period (47 weeks). The study was stopped prematurely after all patients had been randomized (403 patients), due to the Sponsor's decision to discontinue the rimonabant development program. The monitoring therefore focused on the safety profile, based on the reporting of adverse events, and on the primary efficacy criterion. As a result, the analysis (as defined in the statistical analysis plan) only focused on these data and the results are presented through a synopsis-style report. Appendices attached to this synopsis-style report were chosen to provide the relevant information.			
Methodology: This was a multicenter, randomized, double-blind, 2-arm parallel group study comparing rimonabant 20 mg with placebo in patients with type 2 diabetes.			
Number of patients:	Planned: 360	Randomized: 403	Treated: 402
Evaluated:	Efficacy (intent-to-treat [ITT]): 369	Safety : 402	
Diagnosis and criteria for inclusion: Patients with documented history of type 2 diabetes as defined by 2006 World Health Organization criteria (fasting venous plasma glucose ≥7.0 mmol/L [126 mg/dl] or 2-hour postglucose load venous plasma glucose ≥11.1 mmol/L [200 mg/dl]), HbA_{1c} ≥7.0% and ≤10% at screening, and treated with metformin at a fixed and stable dose ≥1500 mg/day, and no other anti-diabetic agent, for at least the 3 months prior to screening were included in the study.			
Investigational product: Rimonabant Dose: 20 mg tablet once daily Administration: Oral (before breakfast) Batch number: [redacted]			

Duration of treatment: 36 weeks

Duration of observation: Approximately 49 weeks (including a 2-week screening period, 36-week double-blind treatment period and 75-day posttreatment follow-up)

Reference therapy: Placebo

Dose: Not applicable

Administration: Oral (before breakfast)

Batch number: [redacted]

Criteria for evaluation:

Efficacy: Only the primary criterion was analyzed: absolute change in HbA_{1c} from baseline to 36 weeks.

Safety: Only adverse events were reviewed and described.

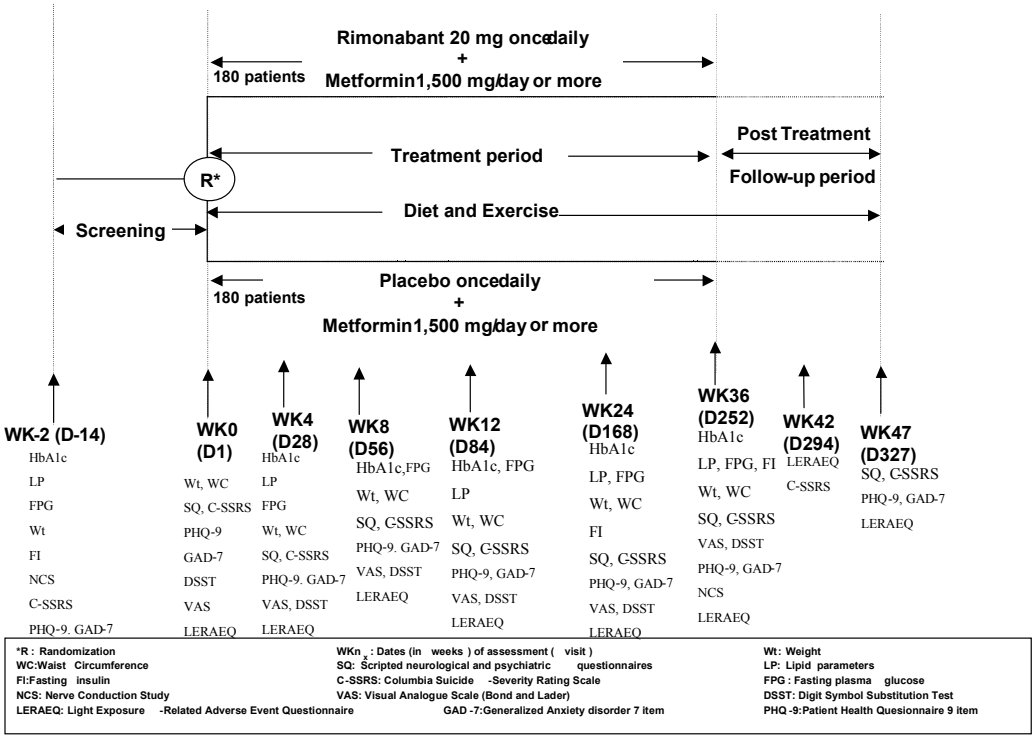
Statistical methods:

Efficacy: The change in HbA_{1c} from baseline to week 36 was analyzed using an analysis of covariance model with last observation carried forward (LOCF ANCOVA), with treatment (rimonabant or placebo), randomization stratum ($7\% \leq HbA_{1c} < 8.5\%$ or $8.5\% \leq HbA_{1c} \leq 10\%$) and region (North America, Europe, and the rest of the world) as fixed effects and baseline assessment as covariate. Means and adjusted means were provided as well as 95% confidence intervals (CI) for adjusted mean differences between rimonabant and placebo.

Safety: Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1 and summarized by treatment group, using descriptive statistics.

Summary:

A summary of the study design is provided below, and a study flow-chart (per protocol amendment) is provided in Figure 1 after the synopsis.



Summary of populations: Table 1 summarizes the randomized and exposed populations.

Table 1 - Summary of patient populations – n (%) - randomized population

	PLACEBO (N=201)	SR141716 20 MG (N=202)	Overall (N=403)
Randomized patients	201 (100%)	202 (100%)	403 (100%)
ITT population[(a)]	181 (90.0%)	188 (93.1%)	369 (91.6%)
Randomized and exposed patients (safety)	200 (99.5%)	202 (100%)	402 (99.8%)

Note: % calculated using the number of randomized patients as denominator
(a): randomized and exposed patients with at least one value at baseline and post baseline of HbA1c (primary efficacy parameter)

Patient disposition: All randomized patients were exposed to at least 1 dose of investigational product, except one patient in the placebo group who was not treated. None of the patients completed the study as planned. Most patients discontinued treatment as a result of the premature stop of the study and were counted in the category "other reason". Table 2 summarizes patient disposition including reasons for treatment discontinuation.

Table 2 - Summary of patient disposition – end-of-treatment – n (%) - randomized population

Patients randomized	PLACEBO (N=201)	SR141716 20 MG (N=202)
Randomized but not treated	1 (0.5%)	0
Randomized and treated	200 (99.5%)	202 (100%)
Completed study treatment period	0	0
Did not complete study treatment period	200 (99.5%)	202 (100%)
Main reason for treatment discontinuation		
Adverse event	1 (0.5%)	6 (3.0%)
Lack of efficacy	1 (0.5%)	0
Poor compliance to protocol	0	0
Lost to follow-up	0	0
Other reason	198 (98.5%)	196 (97.0%)

Note: % calculated using the number of randomized patients as denominator
Category adverse event includes all AEs, TEAE or not.

Exposure: The safety population in this study included 402 patients randomized and exposed to at least 1 dose of the investigational product. The mean number of days patients were exposed to the investigational products was similar in the 2 treatment groups (52.5 days for the 20 mg rimonabant group and 52.9 days for the placebo group). Patient exposure, based on the safety population, is presented in Table 3.

Table 3 - Summary of exposure to study drug - safety population

	PLACEBO (N=200)	SR141716 20 MG (N=202)
Cumulative exposure (patient years)	29.0	29.1
Extent of exposure (days)		
Number	200	202
Mean (SD)	52.9 (26.2)	52.5 (28.9)
Median	47.5	45.0
Min : Max	15 : 142	2 : 191
Number (%) of patients during time periods of interest		
1 - 28 days	38 (19.0%)	43 (21.3%)
29 - 84 days	129 (64.5%)	126 (62.4%)
85 - 168 days	33 (16.5%)	32 (15.8%)
169 - 252 days	0	1 (0.5%)
≥ 253 days	0	0

Note: % calculated using the number of randomized and exposed patients as denominator

Demographics: Patient demographic characteristics were comparable between the 2 treatment groups and are presented in Table 4.

Table 4 - Summary of patient demographics at baseline - safety population

	PLACEBO (N=201)	SR141716 20 MG (N=202)	All (N=403)
Age (years)			
Number	201	202	403
Mean (SD)	55.4 (9.4)	54.8 (9.2)	55.1 (9.3)
Median	57.0	55.5	56.0
Min : Max	26 : 76	22 : 78	22 : 78
[18-44]	20 (10.0%)	27 (13.4%)	47 (11.7%)
[45-64]	148 (73.6%)	147 (72.8%)	295 (73.2%)
≥ 65	33 (16.4%)	28 (13.9%)	61 (15.1%)
Gender, n(%)			
Number	201	202	403
Male	81 (40.3%)	92 (45.5%)	173 (42.9%)
Female	120 (59.7%)	110 (54.5%)	230 (57.1%)
Race, n(%)			
Number	201	202	403
Caucasian/White	163 (81.1%)	166 (82.2%)	329 (81.6%)
Black	2 (1.0%)	1 (0.5%)	3 (0.7%)
Asian/Oriental	20 (10.0%)	21 (10.4%)	41 (10.2%)
Other	16 (8.0%)	14 (6.9%)	30 (7.4%)
Ethnicity in US[a], n(%)			
Number	17	17	34
American Hispanic	4/17 (23.5%)	7/17 (41.2%)	11/34 (32.4%)
American non Hispanic	13/17 (76.5%)	10/17 (58.8%)	23/34 (67.6%)
Waist circumference (cm)			
Number	200	202	402
Mean (SD)	109.3 (15.0)	109.2 (13.8)	109.2 (14.4)
Median	108.1	108.0	108.1
Min : Max	75 : 164	81 : 163	75 : 164
For men, n(%)			
≤ 102 cm	19 (23.8%)	22 (23.9%)	41 (23.8%)
> 102 cm	61 (76.3%)	70 (76.1%)	131 (76.2%)
For women, n(%)			
≤ 88 cm	11 (9.2%)	4 (3.6%)	15 (6.5%)
> 88 cm	109 (90.8%)	106 (96.4%)	215 (93.5%)
Height (cm)			
Number	201	201	402
Mean (SD)	165.2 (10.0)	167.2 (10.1)	166.2 (10.1)
Median	165.0	167.0	165.5
Min : Max	142 : 196	142 : 199	142 : 199
Weight (kg)			
Number	201	202	403
Mean (SD)	93.5 (20.9)	94.5 (20.2)	94.0 (20.5)
Median	91.1	91.9	91.5
Min : Max	53 : 184	57 : 190	53 : 190
BMI (kg/m^2)			
Number	201	201	402
Mean (SD)	34.1 (6.3)	33.7 (6.2)	33.9 (6.2)
Median	33.2	32.6	32.9
Min : Max	19 : 56	23 : 56	19 : 56
< 27	20 (10.0%)	16 (8.0%)	36 (9.0%)
[27-30[	32 (15.9%)	47 (23.4%)	79 (19.7%)
[30-35[	72 (35.8%)	71 (35.3%)	143 (35.6%)
[35-40[	43 (21.4%)	40 (19.9%)	83 (20.6%)
≥ 40	34 (16.9%)	27 (13.4%)	61 (15.2%)
HbA_{1c}[b]			
Number	201	202	403
≥ 7.0% to < 8.5%	145 (72.1%)	146 (72.3%)	291 (72.2%)
≥ 8.5% to ≤ 10.0%	56 (27.9%)	56 (27.7%)	112 (27.8%)

Note: % calculated using the number of randomized patients as denominator; (a): percentage based on US citizens; (b): based on value of HbA_{1c} at baseline

Efficacy results: Mean HbA_{1c} values in both treatment groups were comparable at baseline. Given the short exposure to investigational product, no significant difference between groups was observed in the absolute change in HbA_{1c} from baseline to Week 36 (LOCF) in the ITT population as presented in Table 5.

Table 5 – Mean change and mean difference from baseline in HbA1c at Week 36 - ITT population

HbA_{1c}(%)	PLACEBO (N=181)	SR141716 20 MG (N=188)	p-value
Baseline Result			
Number	181	188	
Mean (SD)	8.06 (0.76)	8.05 (0.79)	
Median	7.90	7.90	
Min : Max	7.0 : 9.9	7.0 : 9.9	
Week 36 (LOCF)			
Number	181	188	
Mean (SD)	7.84 (0.99)	7.72 (1.06)	
Median	7.70	7.60	
Min : Max	5.7 : 11.0	5.3 : 11.6	
Change from baseline			
Number	181	188	
Mean (SD)	-0.21 (0.93)	-0.33 (0.87)	
Median	-0.10	-0.30	
Min : Max	-3.4 : 3.4	-3.5 : 2.8	
LSMean (SE)[a]	-0.17 (0.087)	-0.29 (0.085)	
LSMean difference vs PLACEBO[a]			0.2037
Estimate (SE)	-	-0.11 (0.090)	
95% CI	-	(-0.291 to 0.062)	

[a] Using ANCOVA (mixed model)

Safety results:

- **Overview of adverse events**

There was a higher incidence of treatment-emergent adverse events (TEAEs) in the 20 mg rimonabant group compared with the placebo group. The few serious TEAEs and TEAEs leading to discontinuation of investigational product occurred mostly in the 20 mg rimonabant group. There were no deaths in this study. An overview of patients with at least 1 TEAE is presented in Table 6.

Table 6 – Overview of TEAEs - safety population

	PLACEBO (N=200)	SR141716 20 MG (N=202)
Patients with any TEAE	45 (22.5%)	58 (28.7%)
Patients with any serious TEAE	0	2 (1.0%)
Patients with any TEAE leading to death	0	0
Patients with TEAE leading to permanent treatment discontinuation	1 (0.5%)	6 (3.0%)

Notes: TEAE: Treatment Emergent Adverse Event
TEAE includes all adverse events (AEs) with an onset date during treatment period and up to 75 days following the last study drug intake

- **Summary of treatment-emergent adverse events**

The incidence of any reported TEAEs was consistently less than 5% of patients in any treatment group. The most commonly reported TEAEs in the 20 mg rimonabant group belonged to the gastrointestinal disorders system organ class (SOC) (9.4% patients versus 5.5% in the placebo group), then nervous system disorders (7.9% versus 7.0%), and psychiatric disorders (6.9% versus 2.0%). Preferred terms (PT) reported in ≥2% of patients in the rimonabant group with a difference ≥1% with the placebo group were diarrhoea, nausea, insomnia, anxiety, agitation, asthenia, and decreased appetite. All TEAEs are presented by SOC, high level group term (HLGT), high level term (HLT), and PT (Appendix reference not disclosed).

- **Summary of serious adverse events**

Two patients experienced serious TEAEs during this study, both in the rimonabant group. One patient had pneumonia and the other patient experienced erosive oesophagitis, haemorrhoidal haemorrhage, and hypochromic anaemia. Please refer to the CSR Appendix for details presented as narratives.

No suicidal ideation or suicidal behavior were reported on-treatment. Results of the Columbia Suicide-Severity Rating Scale are presented in CSR Appendix.

- **Summary of deaths**

There were no deaths in this study.

- **Summary of treatment-emergent adverse events leading to treatment discontinuation**

Discontinuation of treatment due to TEAEs occurred in 6 patients (3.0%) in the rimonabant group compared with 1 patient (0.5%) in the placebo group. Table 7 summarizes these events by SOC and preferred term.

Table 7 – Number (%) of patients experiencing at least 1 TEAE leading to permanent treatment discontinuation - safety population

Primary System Organ Class Preferred term	PLACEBO (N=200)	SR141716 20 MG (N=202)
Any Class	1 (0.5%)	6 (3.0%)
Gastrointestinal disorders	1 (0.5%)	1 (0.5%)
Diarrhoea	0	1 (0.5%)
Nausea	1 (0.5%)	0
Abdominal pain	0	1 (0.5%)
Nervous system disorders	0	2 (1.0%)
Cognitive disorder	0	1 (0.5%)
Lethargy	0	1 (0.5%)
Psychiatric disorders	1 (0.5%)	3 (1.5%)
Insomnia	0	1 (0.5%)
Nightmare	0	1 (0.5%)
Decreased interest	0	1 (0.5%)
Psychomotor retardation	0	1 (0.5%)
Confusional state	1 (0.5%)	0
General disorders and administration site conditions	0	2 (1.0%)
Asthenia	0	1 (0.5%)
Fatigue	0	1 (0.5%)

Notes: TEAE: Treatment Emergent Adverse Event
TEAE includes all AEs with an onset date during treatment period and up to 75 days following the last study drug intake
n(%) = number and percentage of patients with at least one treatment emergent adverse event. MedDRA version 11.1
Table sorted by decreasing incidence of primary SOC and PT within SOC for all TEAEs. Sorting based on results for Rimonabant 20 mg arm. In case of equal frequency regarding SOC, alphabetical order is used.

Conclusions: [redacted]
Date of report: 13-May-2009