SYNOPSIS

Name of company: **Name of finished product:** **Name of active substance(s):**	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER:** **Volume:** **Page:**	**(For National Authority Use only)**

Title of the study:	A randomized, double-blind, placebo-controlled, parallel-group, fixed-dose (rimonabant 20 mg) multicenter study of long-term glycemic control with rimonabant in treatment-naïve patients with Type 2 diabetes (EFC5825, SERENADE)
Principal Investigator:	[redacted]
Study centers:	Fifty-six active centers in 7 countries [Argentina, Chile, Germany, Hungary, the Netherlands, Poland, and the United States of America (USA)].
Publications:	Not applicable

Study period: Date first patient enrolled: 22 March 2005 Date last patient completed: 10 June 2006	**Phase of development:** Phase 3b (Confirmative)

Objectives:

Primary efficacy: The primary objective was to assess the antidiabetic effect [change from baseline vs placebo in glycosylated hemoglobin (HbA_{1c})] of 20-mg rimonabant on treatment-naïve patients with Type 2 diabetes over a period of 6 months.

Secondary efficacy: The key secondary objectives were to assess the effect of 20-mg rimonabant over a period of 6 months on:

- other markers of glycemic control (fasting glucose, fasting insulin, proinsulin, and C-peptide);
- insulin resistance and ß-cell function [Homeostasis Model Assessment (HOMA) indices];
- body weight; and
- other cardiovascular risk factors [high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and blood pressure (BP)].

Safety: The safety and tolerability of 20-mg rimonabant were evaluated in this population over a period of 6 months.

Methodology: This international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose (20-mg rimonabant, once daily), 6-month study was comprised of a screening period and a double-blind treatment period.

Patients were screened for inclusion and exclusion criteria 1 week before the baseline visit after which they were randomized using a stratification based on initial glycemic control (level of HbA_{1c} at screening as follows: ≥7% to <8.5% and ≥8.5% to ≤10%). The randomization ratio was 1:1. During the 6-month treatment period, a mild hypocaloric diet (600 kcal deficit/day below basal energy expenditure) and increased physical activity were adapted to each patient, reinforced by dietician interviews at baseline and during visits at Months 3 and 6.

Name of company:	**TABULAR FORMAT**	**(For National Authority Use only)**
Name of finished product:	**REFERRING TO PART OF THE DOSSIER:**	
Name of active substance(s):	**Volume:** **Page:**	

Number of patients evaluated:

Summary of patient analysis populations [N (%)]

	Placebo	Rimonabant 20 mg	Overall
Planned	132	132	264
Randomized	141	140	281
Randomized and exposed (safety population)	140	138	278
Intent-to-treat (ITT)	131	130	261
Completers	125	111	236

Diagnosis and criteria for inclusion:

- Male or female patients ≥18 years-of-age;
- diagnosis of Type 2 diabetes for at least 2 months, but no longer than 3 years;
- Type 2 diabetes not previously treated with a pharmacological agent, with some exceptions (please see the body of the report);
- HbA_{1c} ≥7% and ≤10% at the screening visit;
- No weight loss >5 kg within 3 months before screening visit.

Investigational product: Rimonabant

Dose: 20 mg tablet once daily

Administration: Oral administration in the morning, before breakfast

Batch numbers: [redacted]

Duration of treatment: 6 months (±14 days) | **Duration of observation**: 6 months plus 7 to 14 days

Reference therapy: Placebo

Dose: Not applicable

Administration: Oral administration in the morning before breakfast

Batch numbers: [redacted]

Evaluation criteria:

Efficacy:

Primary criteria:

- the absolute change in HbA_{1c} from baseline to Month 6.

Secondary criteria:

- glucose homeostasis and related criteria (fasting plasma glucose, C-peptide, proinsulin, and fasting insulin);
- HOMA analysis;
- body weight;
- HDL-C, TG, and BP.

Safety: Safety was assessed by the evaluation of reported adverse events (AEs), physical examinations including comprehensive neurologic examinations, clinical laboratory tests, and vital signs assessments.

Statistical methods: Efficacy analyses were performed on the intent-to-treat (ITT) population, on the last observation carried forward (LOCF) excluding post-rescue medication assessments. Differences versus baseline were expressed as mean ± standard deviation (SD). Differences versus placebo were expressed in least square mean (LS mean) ± standard error of the LS mean (SEM).

The safety population consisted of all randomized patients who were exposed to at least 1 dose of double-blind investigational product.

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume: Page:	

Statistical methods (continued):

Efficacy: The comparisons of the treatment groups for continuous endpoints at 6 months were conducted using analysis of covariance (ANCOVA). The ANCOVA model included 3 fixed terms (treatment, country, and randomization strata) and the baseline assessment as the covariate. The comparisons of the treatment groups for categorical endpoints at 6 months were conducted using a Cochran-Mantel-Haenszel (CMH) test stratified on randomization stratum and country.

All statistical tests were 2-sided tests at a nominal 5% significance level.

Safety: Safety and tolerance data were summarized by treatment group using descriptive statistics. No statistical tests were planned.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) were defined as AEs that occurred or worsened or became serious during double-blind study treatment exposure or within 5 half-lives (75 days) following the last double-blind investigational product intake. Treatment-emergent AEs were analyzed by system organ class (SOC) and preferred term (PT).

Summary:

Demography: This population of patients with untreated Type 2 diabetes included male (138; 49.6%) and female (140; 50.4%) patients who were 84.2% Caucasian, 2.9% Black, 1.1% Asian, and 11.9% other races. The average age was 56.6 (±10.5) years and the average body mass index (BMI) was 34.5 (±6.7) kg/m^2. Demographic and anthropomorphic characteristics, medical histories, and disease characteristics were similar between groups at baseline with the exception of age distribution of patients, with a greater proportion of elderly (>65 years-of-age) patients in the rimonabant group (14.3% in the placebo group and 24.6% in the rimonabant group).

Efficacy results: During the course of the study, 18 patients received antidiabetic rescue medication [14 in the placebo group (10.0%) and 4 (2.9%) in the 20-mg rimonabant group]. Among these patients, only one (in the 20-mg rimonabant group) was excluded from the efficacy analysis due to the absence of a postbaseline assessment performed before the introduction of the rescue medication. No efficacy assessment performed after the introduction of rescue medication or after the discontinuation of study treatment was included in the efficacy analyses.

For the primary analysis, mean HbA_{1c} values in both treatment groups were comparable at baseline. There was an absolute change from baseline in the rimonabant 20-mg group of -0.8%, compared with a –0.3% change in the placebo group, resulting in an adjusted mean between-treatment difference at 6 months of 0.51% in favor of rimonabant (ie, a greater decrease was seen with rimonabant 20 mg than with placebo), which was highly statistically significant (p=0.0002).

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume:	
	Page:	

Summary (continued):

Efficacy results (continued):

Mean change and mean difference from baseline in HbA_{1c} at 6 months (LOCF excluding post-rescue medication data) – ITT population

HbA_{1c} (%)	**Placebo (N=140)**	**Rimonabant 20 mg (N=138)**	**p-value**
Baseline			
N	131	130	
Mean [standard deviation (SD)]	7.9 (0.7)	7.9 (0.8)	
Median	7.6	7.8	
(Min, Max)	(7.0, 9.7)	(7.0, 9.9)	
Month 6 endpoint			
N	131	130	
Mean (SD)	7.5 (1.3)	7.1 (1.1)	
Median	7.3	6.9	
(Min, Max)	(5.1, 13.9)	(4.8, 11.7)	
Change from baseline			
N	131	130	
Mean (SD)	-0.3 (1.2)	-0.8 (1.2)	
Median	-0.3	-0.7	
(Min, Max)	(-3.0, 4.6)	(-3.6, 4.3)	
LS Mean (SE)	-0.52 (0.12)	-1.03 (0.13)	
LS Mean Difference vs Placebo			
Estimate (SE)	-	-0.51 (0.14)	0.0002
95% [confidence intervals (CIs)]	-	(-0.78, -0.24)	

Statistically significant between-treatment differences at 6 months in favor of the 20-mg rimonabant group were observed for the following secondary efficacy variables when compared with the placebo group:

- HbA_{1c} "responder" analysis (achieved an HbA_{1c} value at 6 months <7%; secondary analysis of the primary variable): 50.8% of the rimonabant group and 35.1% of the placebo group (p=0.0122);
- fasting plasma glucose (FPG): mean changes from baseline of –0.9 mmol/L in the rimonabant group compared with +0.1 mmol/L in the placebo group (p=0.0012);
- proinsulin: mean changes from baseline of –23.6 pmol/L in the rimonabant group compared with –9.1 pmol/L in the placebo group (p=0.0041);
- insulin resistance: mean changes from baseline of –1.89% in the rimonabant group compared with +0.33% in the placebo group (p=0.0098);
- body weight: mean changes from baseline of –6.7 kg in the rimonabant group compared with –2.8 kg in the placebo group (p<0.0001);

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume: Page:	

Summary (continued):

Efficacy results: (continued)

- HDL-C: mean percent change from baseline of 10.05% in the rimonabant group compared with 3.15% in the placebo group ($p<0.0001$);
- TG: mean percent change from baseline of –16.33% in the rimonabant group compared with +4.35% in the placebo group ($p=0.0031$);
- TG values for patients with hypertriglyceridemia at baseline: mean percent change from baseline of –25.10% in the rimonabant group compared with –5.47% in the placebo group ($p=0.0006$).

In addition, clear trends toward greater reductions in the rimonabant group compared with the placebo group in fasting plasma insulin and greater improvements in beta-cell function (as measured by HOMA-β) were observed.

There was a significant treatment-by-age interaction in the primary analysis, HbA_{1c} change from baseline, in which the HbA_{1c} treatment effect was reduced with increasing age. Further examination revealed that this result was due to the atypically large mean HbA_{1c} reduction from baseline (0.9%) in the 20 patients aged >65 years in the placebo group. This was an atypical result both for other variables in this study and in other trials of rimonabant in type 2 diabetic patients, and is of doubtful significance.

Safety results:

The number (%) of randomized and exposed patients who experienced at least 1 treatment-emergent adverse event (TEAE) is presented in the following table.

	Placebo (N=140) N (%)	**Rimonabant 20 mg (N=138) N (%)**
Patients with any TEAE	81 (57.9)	97 (70.3)
Patients with any SAE	5 (3.6)	9 (6.5)
Deaths	1 (0.7)	0 (0)
Patients permanently discontinued due to a TEAE	3 (2.1)	13 (9.4)

Name of company:	TABULAR FORMAT	(For National Authority Use only)
Name of finished product:	REFERRING TO PART OF THE DOSSIER:	
Name of active substance(s):	Volume: Page:	

Summary (continued):

Safety results:

The percentage of patients who had at least 1 TEAE, serious adverse event (SAE), and permanent discontinuations due to TEAEs were higher in the rimonabant 20 mg group compared to the placebo group. There were more TEAEs reported in the nervous system, gastrointestinal, psychiatric, and general disorders system organ classes (SOCs) in the rimonabant group; dizziness, nausea, upper respiratory tract infection, anxiety, depressed mood, vertigo, and vomiting being the more commonly reported events.

In the rimonabant 20-mg group, the percentages of patients reporting events of dizziness, nausea, upper respiratory tract infection, anxiety, depressed mood, vertigo, vomiting, decreased visual acuity, dry mouth, hypoesthesia, and asthenia were higher in the rimonabant group compared with the placebo group. Although depressed mood was more common in the rimonabant group, depression, which is a more severe categorization than depressed mood, was more common in placebo patients. There were only 2 reported episodes of hypoglycemia in the study, 1 in each treatment group, both nonsevere.

In the placebo group, the percentages of patients reporting headache, nasopharyngitis, constipation, pharyngitis streptococcal, pneumonia, and asthma were higher compared to the rimonabant 20-mg group.

A total of 14 patients [9 patients (6.5%) in the rimonabant group and 5 patients (3.6%) in the placebo group] experienced a total of 20 SAEs. The Investigators determined that all events were unrelated to the investigational product. No particular pattern to the occurrence of these SAEs was detected.

There was a single death during the study, in the placebo group, due to brainstem hemorrhage.

The incidence of TEAEs leading to permanent discontinuation was greater in the 20 mg rimonabant group than in the placebo group, mainly because of TEAEs in the gastrointestinal, nervous system, and psychiatric SOCs. The most frequently reported TEAEs leading to treatment discontinuation in the rimonabant group were depressed mood, nausea, paresthesia, anorexia, dizziness, and hyposmia.

Infrequent potentially clinically significant abnormalities (PCSAs) for laboratory parameters and vital signs were observed in the placebo and rimonabant groups and were generally similar between the 2 groups.

Name of company: Name of finished product: Name of active substance(s):	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER:** **Volume:** **Page:**	**(For National Authority Use only)**

Summary (continued):

Conclusions: [redacted]

Date of report: 06 December 2006