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Sponsor/Company: sanofi-aventis **Drug substance**: Rimonabant (SR141716)	**Study Identifier**: NCT00288236 **Study code**: EFC5593

Title of the study:

A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Fixed-Dose Study Evaluating the Effect of One Dose of Rimonabant (20 mg/day) on Glycemic Control in Type 2 Diabetic Patients Inadequately Controlled with Insulin (ARPEGGIO).

Study centers:

Multicenter with a total of 60 centers in 12 countries (Argentina, Australia, Canada, Chile, France, Germany, Italy, Netherlands, Russia, South Africa, the United Kingdom, and the United States of America).

Study period:

Date first patient enrolled: 10-Jan- 2006

Date last patient completed: 20-Jul- 2007

Phase of development: Phase 3b

Objectives:

The primary objective of this study was to assess the effect of rimonabant on glycosylated hemoglobin (HbA1c) over a period of 48 weeks (336 days) in patients with Type 2 diabetes treated with insulin.

The secondary objectives were to assess the effect of rimonabant over a period of 48 weeks (336 days) in patients with Type 2 diabetes treated with insulin on body weight, lipid profile, abdominal obesity, safety and tolerability.

Methodology:

Multicenter, randomized, 2-arm, placebo-controlled, double-blind, parallel-group, fixed-dose (20 mg rimonabant) versus placebo

Number of patients:

Summary of patient analysis population

		Rimonabant	
	Placebo	**20 mg**	**Overall**
Planned	150	150	300
Randomized	187	181	368
Randomized and exposed (safety population)	187	179	366
Intent-to-treat (ITT)[a]	186	179	365
Per-protocol population	92	112	204

[a] The ITT population included all randomized and exposed patients who had a baseline and postbaseline assessment of any one of the efficacy parameters

Diagnosis and criteria for inclusion:

Patients with Type 2 diabetes treated with insulin (≥30 U/day for at least 4 weeks) with HbA1c ≥7% and ≥18 years of age.

Investigational product: Rimonabant

Dose: 20 mg-tablet once daily

Administration: oral administration in the morning before breakfast
Reference therapy: Placebo
Dose: Not applicable
Administration: oral administration in the morning before breakfast
Duration of treatment: up to 336 days (+10 days) **Duration of observation:** 350 days (+10 days)
Criteria for evaluation: Efficacy: The primary efficacy measure was change in HbA1c from baseline to the end of the study (Day 336). The secondary efficacy measures were change from baseline to the end of the study in fasting plasma glucose, percentage of patients with HbA1c <7% and <6.5% at the end of the study, change from baseline to the end of the study in body weight, percent change from baseline to the end of the study in high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), change from baseline to the end of the study in waist circumference, total daily insulin dose, proportion of patients with a decrease in total daily insulin dose by >10% of the baseline daily dose at any time during the study, introduction of rescue medication at any time during the study, number of days from baseline to the end of the study with at least 1 nonsymptomatic hypoglycemia, and other lipid parameters: percent change from baseline to the end of the study in total cholesterol (Total-C) and low-density lipoprotein cholesterol (LDL-C), and change from baseline to the end of the study in total-C/HDL-C ratio. Safety: Safety assessment were comprised of physical examinations, vital signs, laboratory tests, adverse events (AEs) including neurological and psychiatric AEs, and hypoglycemia.
Statistical methods: Efficacy: All efficacy analyses were performed on the ITT population excluding efficacy assessments obtained after the patients discontinued treatment for 7 days or more and/or after the use of rescue medication. If a patient discontinued treatment or the study prematurely, or did not have his/her measurement at the Day 336 visit, the last observation carried forward (LOCF) procedure was utilized. The primary endpoint, change from baseline to the end of the study (Day 336) in HbA1c, was analyzed using an analysis of covariance (ANCOVA) model with treatment (rimonabant or placebo), randomization stratum (7% ≤HbA1c <8.5% or 8.5% ≤HbA1c) and country as fixed effects and using the baseline assessment as the covariate. Both means and adjusted means are provided as well as 95% confidence intervals (CIs) constructed for adjusted mean differences between rimonabant and placebo. All statistical tests were 2-sided tests at a nominal 5% significance level. Safety: The safety population consisted of all randomized patients who were exposed to at least 1 dose of double-blind investigational product. Safety and tolerance data were summarized by treatment group using descriptive statistics. Adverse events (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 study treatment exposure or within 5 half-lives (75 days) following the last intake of investigational product.

Summary:

Demography:

The overall population included 157 males (42.9%) and 209 females (57.1%) and the majority of patients were Caucasian (77.0%). The mean age was 57.8 (±10.4) years and the average body mass index was 34.61 (± 6.45) kg/m^2. Demographic and anthropomorphic characteristics, medical histories, and other disease characteristics were similar between groups at baseline.

Efficacy:

Mean HbA1c baseline values were comparable between groups, 9.12% for patients in the rimonabant group and 9.09% for patients in the placebo group. For the primary efficacy analysis, a statistically significant reduction in HbA1c from baseline was found in the rimonabant group compared to the placebo group (-0.86% versus -0.22%, p<0.0001), resulting in a mean treatment difference of -0.64% in favor of rimonabant.

In addition, compared to placebo, treatment with rimonabant resulted in a significantly higher proportion of patients who achieved an HbA1c value <7% (p=0.0012) and <6.5% (p=0.0020), showed significantly reduced fasting plasma glucose levels (p=0.0193), resulting in a mean treatment difference of -0.88 mmol/L, a significant loss in body weight (-2.56 kg, p<0.0001), a significant decrease in waist circumference (-2.47 cm, p<0.0001), significant increase in HDL-C and decrease in TG (10.4%, p<0.0001 and 11.8%, p=0.0235, respectively), and reduced insulin dose (total daily reduction >10%), with 16.8% in rimonabant-treated patients and 6.0% in placebo-treated patients.

Safety:

Treatment emergent adverse events were reported frequently during the study with comparable rate between the rimonabant and placebo groups (87.7% versus 85.6%, respectively). The most frequently reported TEAEs in both groups were metabolism and nutrition disorders with a higher rate in the rimonabant group compared to the placebo group (57.0% and 49.2%, respectively).

Treatment-emergent adverse events reported by at least 5% of patients in the rimonabant group and more frequently (≥1%) than in the placebo group were hypoglycemia (56.4% versus 47.1%), anxiety (14.0% versus 5.3%), depression (10.1% versus 4.3%), dizziness (10.1% versus 8.0%), nausea (11.2% versus 1.6%), insomnia (7.8% versus 3.2%), paresthesia (6.7% versus 4.8%), and nasopharyngitis (5.6% versus 4.3%).

Fewer patients in the rimonabant group compared with the placebo group experienced serious TEAEs (16.8% versus 19.3%, respectively). No particular pattern in the occurrence of these serious TEAEs was detected. The most common serious TEAE was hypoglycemia (2 in the placebo group and 4 in the rimonabant group). Similar number of patients in the rimonabant and placebo groups reported severe hypoglycemia (8 and 7 patients, respectively). There were 2 deaths during the study, both in the placebo group.

More patients in the rimonabant group permanently discontinued due to TEAEs compared with the placebo group (17.3% versus 8.0%, respectively). The most frequently reported TEAEs in the rimonabant group leading to treatment discontinuation were nausea, anxiety, and depression.

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