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Sponsor / Company: sanofi-aventis **Drug substance(s):** SR141716 (rimonabant)	**Study Identifier:** NCT00325546 **Study code:** EFC6001

Title of the study:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-dose (rimonabant 20mg), Multi-national, Multicenter Study of Weight-Reducing Effect and Safety of Rimonabant in Obese Patients With or Without Comorbidities.

Study center(s): Multicenter study with 32 sites in China (12), Korea (11) and Taiwan (9)

Study period:

Date first patient enrolled: 07 Apr 2006

Date last patient completed: 24 Apr 2007

Phase of development: Phase 3

Objectives:

Efficacy:
Primary objective of this study was to assess the effect of rimonabant on weight loss and weight maintenance over a period of 9 months when prescribed with a hypocaloric diet in obese patients with or without comorbidities.
Secondary objectives were to assess the effect of rimonabant over a period of 9 months on high density lipoprotein-cholesterol (HDL-cholesterol), triglycerides, fasting insulin, fasting glucose, and waist circumference.

Safety:
Safety assessments were the evaluation the safety and tolerability of rimonabant over a period of 9 months.

Methodology:

Multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study over a period of 9 months Following a screening period of 7 to 14 days, eligible patients were centrally randomized via an interactive voice response system in a 1:1 ratio to rimonabant 20 mg or placebo at the baseline visit and treated in a double-blind fashion for 9 months. The randomization was stratified by center and body mass index (BMI) status at baseline (BMI ≥25 to 27 kg/m^2 or BMI >27 kg/m^2). A mild hypocaloric diet was prescribed during the double-blind treatment period. After randomization patients were seen every 28 days up to 9 months (Day 252).

Number of patients:
The number of patients planned for this study is shown in the table below.

	Placebo	Rimonabant 20 mg	Overall
Planned	320	320	640
Randomized	325	318	643
Randomized and exposed (safety population)	324	318	642
Intent-to-treat (ITT)*	317	315	632

*ITT population for weight

Diagnosis and criteria for inclusion:
Inclusion criteria included:

- Patients ≥18 years of age
- Body mass index ≥25 kg/m^2
- Stable weight (variation <5 kg) within 3 months before screening visit.

Investigational product: Rimonabant

Dose: 20 mg once daily

Administration: Oral, in the morning before breakfast

Duration of treatment: Approximately 9 months ± 2 weeks

Duration of observation: Maximum of 10 months

Reference therapy: Placebo

Dose: not applicable

Administration: Oral, in the morning before breakfast

Criteria for evaluation:

Efficacy:

The primary efficacy assessment was absolute change in body weight from baseline (Day 1) to Day 252.
The secondary confirmatory efficacy assessments were absolute and relative change from baseline at 9 months in HDL-cholesterol, and triglycerides, and absolute change from baseline at 9 months in fasting insulin, and fasting plasma glucose.

Safety:

The safety assessment included spontaneously reported adverse events, clinical examinations, laboratory tests, vital signs, and electrocardiograms.

Statistical methods:

Efficacy analyses were performed on the last observation carried forward (LOCF) at 9 months using patients in the ITT population, which consisted of all randomized patients.

The primary efficacy endpoint was the absolute change in body weight from baseline to 9 months and was analyzed using a 3-way analysis of covariance (ANCOVA) model. The model included 3 fixed effects, treatment, country/region, and randomization stratum (BMI 25 to 27 kg/m² or >27 kg/m² at baseline), and 1 covariate, baseline weight. Rimonabant 20 mg was compared to placebo using a Student's t-test within the framework of the ANCOVA model. In addition, a 95% confidence interval (CI) was constructed for the difference in mean absolute weight changes between rimonabant 20 mg and placebo. Similar analyses were applied to the secondary efficacy endpoints.

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

All adverse events were coded by sanofi-aventis Clinical Data Management Department using Medical Dictionary for Regulatory Activities (MedDRA, Version 10.0). Treatment-emergent adverse events were defined as adverse events that occurred or worsened during double blind study treatment exposure or within 5 half-lives (75 days) following the last double-blind investigational product intake and were analyzed by system organ class and preferred term. No statistical tests were planned to be performed.

Summary:

Demography and baseline characteristics**:**

A total of 643 patients were randomized (318 patients in the rimonabant 20 mg group and 325 patients in the placebo group) from 32 centers in China, Republic of Korea, and Taiwan. Of the 643 randomized patients, 642 patients (318 patients in the rimonabant 20 mg group and 324 patients in the placebo group) were exposed to at least 1 dose of the investigational product. A higher percentage of patients in the rimonabant 20 mg group (89.6%) completed the study treatment period compared with the placebo group (81.5%). More than two-thirds of the patients were women (68.5%), and 568 (88.5%) of the 642 randomized and exposed patients were less than 50 years of age, with a mean age of 36.0 (±10.7) years. The mean baseline BMI was 30.3 (±4.2) kg/m^2, and the BMI ranged from 23.9 to 52.2 kg/m^2 with a majority of the patients (78.0%) having a BMI >27 kg/m^2. The mean baseline body weight was 81.5 (±15.7) kg, and the mean baseline waist circumference was 96.9 (±11.1) cm. Demographic and anthropomorphic characteristics, medical histories, and disease characteristics were similar between the 2 treatment groups at baseline. In addition, the number of patients was distributed equally across the country/region between the 2 treatment groups.

Efficacy:

At 9 months, in the ITT population, rimonabant 20 mg decreased weight by 2.99 kg (95% CI: -3.704, -2.266) more when compared with the placebo (p <0.0001). The results are summarized in the table below.

Weight (kg)	**Placebo (N = 325)**	**Rimonabant 20 mg (N = 318)**
Baseline		
Number	317	315
Mean (SD)	81.99 (16.55)	80.91 (14.88)
Change from baseline		
Mean (SD)	-1.85 (4.25)	-4.81 (5.05)
LS Mean (SEM)	-1.74 (0.291)	-4.72 (0.295)
LS Mean Difference (SEM)	-	-2.99 (0.366)
95% CI	-	(-3.704 to -2.266)
P-value	-	<0.0001
Percent change from baseline		
Mean (SD)	-2.25 (4.86)	-6.00 (6.03)

N = population size; SD = standard deviation; LS = least square; SEM = standard error of the mean; CI = confidence interval

The percentage of patients (ITT population) who achieved at least a 5% reduction and 10% reduction from their baseline bodyweight at 9 months was also significantly greater in the rimonabant 20 mg group (53.0% and 20.0%, respectively) than the placebo group (21.5% and 5.7%, respectively) (p<0.001 for both).

Statistically significant between-treatment differences at 9 months in favor of the rimonabant 20 mg group were observed for the following secondary efficacy variables when compared with the placebo group:

- HDL-cholesterol: mean percent change from baseline was increased by 10.1% in the rimonabant 20 mg group when compared with 3.0% in the placebo group (7.1% versus placebo) (p <0.0001)
- Triglycerides: mean percent change from baseline was decreased by -8.7% in the rimonabant 20 mg group compared with an increase of 1.9% in the placebo group (-10.6% versus placebo) (p = 0.0047)
- Waist circumference: mean change from baseline was decreased by -5.9 cm in the rimonabant 20 mg group compared with -3.1 cm in the placebo group (-2.8 cm versus placebo) (p <0.0001).

For fasting glucose and fasting insulin, minimal changes from baseline at 9 months were observed in both treatment groups.

Safety results:

The number and percent of randomized and exposed patients who experienced at least 1 treatment-emergent adverse event is presented in the following table:

	Placebo (N=324)	Rimonabant 20 mg (N=318)
Patients with any TEAE	184 (56.8%)	210 (66.0%)
Patients with any serious TEAE	15 (4.6%)	10 (3.1%)
Patients with any TEAE leading to death	0	0
Patients permanently discontinued due to TEAE	9 (2.8%)	10 (3.1%)

N = population size; TEAE = treatment-emergent adverse event

The percentage of patients who had at least 1 treatment-emergent adverse event was higher in the rimonabant 20 mg group than in the placebo group. However, serious treatment-emergent adverse events were more frequently reported in the placebo group than in the rimonabant 20 mg group.

The most common adverse events reported with an incidence ≥2% in rimonabant-treated patients and ≥1% in placebo-treated patients were as follows: upper respiratory tract infection, nausea, diarrhea, dyspepsia, vomiting, dizziness, depression, anxiety, insomnia, hyperhidrosis, palpitations, and fatigue.

In the placebo group, the most common adverse events reported with an incidence ≥2% (and ≥1% over rimonabant patients) were nasopharyngitis, constipation, abdominal pain, abdominal pain upper, and headache.

A total of 25 patients, 10 patients (3.1%) in the rimonabant 20 mg group and 15 patients (4.6%) in the placebo group experienced a total of 28 serious adverse events. The Investigators determined that all events except 1 (embolic cerebral infarction in a placebo patient) were not related to the investigational product. No particular pattern in the occurrence of these serious adverse events was detected.

No deaths were reported during the study.

The incidence of treatment-emergent adverse events leading to permanent discontinuation was low and comparable in both treatment groups.

Potentially clinically significant abnormalities for laboratory parameters and vital signs were low, infrequent, and generally similar between the 2 treatment groups.

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