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Sponsor/Company: sanofi-aventis **Drug substance**: Rimonabant (SR141716)	**Study Identifier**: NCT00239967 **Study code**: EFC5823

Title of the study:
A randomized, double-blind, two-arm placebo-controlled, parallel-group, multicenter study of rimonabant 20 mg once daily in the treatment of atherogenic dyslipidemia in abdominally obese patients (ADAGIO).

Study centers:
Multicenter, international study with a total of 53 centers in 14 countries (Australia, Brazil, Canada, Denmark, Hong Kong, Italy, South Korea, Malaysia, Mexico, Singapore, South Africa, Sweden, Taiwan, and the United States of America).

Study period:

Date first patient enrolled: 31-May-2005

Date last patient completed: 22-Feb-2007

Phase of development: Phase 3b

Objectives:
The primary objective was to assess the effect of rimonabant 20 mg on high-density lipoprotein cholesterol (HDL-C) and tri-glyceride (TG) plasma levels over a period of 1 year when prescribed in conjunction with a hypocaloric diet (600 kcal deficit per day) in abdominally obese patients with atherogenic dyslipidemia.

The secondary objectives were to assess the effect of 20 mg rimonabant over a period of 1 year on waist circumference, body weight, visceral fat measured using computed tomography (CT) scan in a subgroup of patients, insulin resistance (using HOMA formulae), fasting glucose, fasting insulin, and glycosylated hemoglobin (HbA1c), adiponectin and leptin, liver fat measured using CT scan in a subgroup of patients, specific lipid parameters, and high-sensitivity C-reactive protein (hs-CRP).

The safety and tolerability of 20 mg rimonabant were evaluated in this population over a period of 14 months (±7 days) including a 2-month posttreatment follow-up visit.

Methodology:
International, multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel-group, fixed-dose study that comprised of 3 periods: a screening period up to 7 days ± 4 days, a treatment period of 12 months ± 14 days, and a posttreatment follow-up period of 2 months ± 7 days.

Number of patients:

Summary of patient analysis population

	Placebo	Rimonabant 20 mg	Overall
Planned	370	370	740
Randomized	397	406	803
Randomized and exposed (safety population)	395	404	799
Intent-to-treat (ITT)[a]	387	393	780
ITT – CT scan subpopulation	114	117	231
Completers	278	297	575

[a] The IIT population included all patients with at least 1 postbaseline efficacy assessment regardless of the parameter.

Diagnosis and criteria for inclusion:

Male or female patients ≥18 years of age with waist circumference >102 cm in men and >88 cm in women, dyslipidemia consisting of triglyceridemia ≥1.50 g/L (1.69 mmol/L) and ≤7.0 g/L (7.90 mmol/L) and/or HDL-C <50 mg/dL (1.29 mmol/L) in women and <40 mg/dL (1.04 mmol/L) in men.

Investigational product: Rimonabant

Dose: 20 mg-tablet once daily

Administration: Oral administration in the morning with or without food

Reference therapy: Placebo

Dose: Not applicable

Administration: Oral administration in the morning with or without food

Duration of treatment: 12 months

Duration of observation: approximately 14 months

Criteria for evaluation:

Efficacy:

The primary efficacy criteria were relative changes in HDL-C from baseline to Month 12 and relative changes in TG from baseline to Month 12.

The main secondary efficacy criterion was waist circumference and other secondary efficacy criteria were body weight, insulin resistance as calculated by the Homeostasis Model Assessment (HOMA) analysis, and abdominal fat (visceral fat, subcutaneous fat and visceral/subcutaneous fat ratio).

Safety:

Safety assessments were comprised of physical examinations, vital signs, laboratory tests, adverse events (AEs) including neurological and psychiatric AEs.

Statistical methods:

All efficacy analyses were performed on the ITT population and excluded assessments obtained after the patients discontinued treatment (up to 1 day after treatment discontinuation). If a patient discontinued treatment prematurely or did not have a measurement at the Month 12 (V8) visit, the last observation carried forward (LOCF) procedure was utilized, analyzing the last postbaseline value. The primary analysis for the 2 coprimary endpoints was performed using the ITT population and excluding values, of the analyzed parameter, obtained after any lipid-lowering treatment change.

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

For the 2 coprimary efficacy endpoints, percent change from baseline to Month 12 in HDL-C and TG, each endpoint was analyzed using an analysis of covariance (ANCOVA) with treatment (rimonabant or placebo) and randomization stratum (use/no use of lipid-

modifying agents at the screening visit) as fixed effects and using baseline assessment as the covariate. Placebo-adjusted least-square (LS) means and confidence intervals (CIs) were estimated within the framework of ANCOVA. All statistical tests were 2-sided tests at a nominal 5% significance level.

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 and preferred term.

Summary:

Demography:

In this study, the gender ratio was balanced (46.4% males and 53.6% females) and the majority of patients were Caucasian. The average age was 49.6 (±11.8) years and the average body mass index was 36.2 (±6.3) 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 the patients, with a greater proportion of elderly patients (>65 years of age) in the rimonabant group (11.4%) versus placebo group (6.6%).

Efficacy results:

For the primary efficacy criteria, rimonabant significantly increased HDL-C (+7.37% over placebo, p<0.0001) and significantly decreased TG (-17.99% over placebo, p <0.0001) (see table below).

At 12 months, statistically significant differences between the rimonabant- and placebo-treated patients were observed for waist circumference (-2.84 cm, p<0.0001), body weight (-3.61 kg, p<0.0001), decrease in total adipose tissue (7.0%, p=0.0003), decrease in visceral adipose tissue (10.1%, p=0.0003), decrease in subcutaneous adipose tissue (5.1%, p=0.0043), decrease in the ratio visceral fat to subcutaneous fat (p=0.0422), and insulin resistance (p=0.0046).

Safety results:

Treatment-emergent AEs were more frequently reported in the rimonabant group than in the placebo group. The most frequently reported TEAEs in rimonabant–treated patients compared to placebo-treated patients were nausea (21.3% versus 5.8%), dizziness 16.6% versus 11.9%), anxiety (15.1% versus 11.6%), diarrhea (12.6% versus 9.4%), insomnia (11.6% versus 8.6%), influenza (11.4% versus 9.4%), fatigue (8.2% versus 4.3%), depression (7.7% versus 6.3%), and depressed mood (6.9% versus 5.1%). The proportion of patients who reported serious AEs during the study was similar in the 2 treatment groups, 29 patients (7.2%) in the rimonabant and 29 patients (7.3%) in the placebo group. No particular pattern in the occurrence of these serious AEs was detected. No deaths were reported during the study. The percentages of patients who prematurely discontinued study treatment due to TEAEs were higher in the rimonabant group compared with the placebo group. The most frequently reported TEAEs in the rimonabant group that led to treatment discontinuation were anxiety, depression, and nausea.

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

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