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Sponsor/Company: sanofi-aventis **Drug substance**: Rimonabant (SR141716)	**Study Identifier**: NCT00459173 **Study code**: EFC4796

Title of the study:
Comparison of the efficacy and safety of 2 oral doses of rimonabant, 5 mg/day or 20 mg/day, versus placebo, as an aid to maintenance of smoking cessation [STRATUS-WW (worldwide)].

Study centers:
Multicenter, international study with a total of 53 active centers in Australia, Canada, and the United States.

Study period:

Date first patient enrolled:	25-Nov-2002
Date last patient completed:	16-Jun-2004 (Visit 23, Week 32) 02-Dec-2004 (Visit 29, Week 58) 23-Sep-2005 (1-year follow-up)

Phase of development: Phase 3

Objectives:
The primary objective was to evaluate the efficacy of 2 dose levels of rimonabant (stratum 5 mg and stratum 20 mg) for the maintenance of abstinence from smoking.

The secondary objectives were to evaluate the effects of rimonabant on craving and weight, to evaluate the safety and tolerability of 2 doses of rimonabant, to assess the pharmacokinetics (PK) of rimonabant (ie, standard PK evaluation in the population of smokers), and to evaluate quality of life (QOL), respiratory symptom burden, and pharmacoeconomics.

Methodology:
International, multicenter, randomized, double-blind, placebo-controlled, parallelgroup, 2-year study. The study included 2 parallel strata, rimonabant 5 mg and rimonabant 20 mg, and 6 segments, A to F.

Segment A:	Up to 2 weeks prior to randomization;screening period without treatment
Segment B:	2 weeks of double-blind treatment with 5 or 20 mg rimonabant before quitting
Sebment C:	8 weeks of double-blind treatment with 5 or 20 mg rimonabant after quitting. Segment B and C were not placebo-controlled.
Segment D:	Re-randomization of abstainers up to 52 weeks to continue double-blind treatment with 5 mg rimonabant or swtiched to placebo or continue treatment with 20 mg rimonabant or switched to 5 rimonanabnt or placebo.
Segment E:	Between Week 53 and 58, safety observation, no treatment.
Segment F:	Between Week 59 and 102, follow-up period, no treatment.

Number of patients: Total planned 4850

Summary of patient analysis population

	Stratum 5 mg	Stratum 20 mg
Randomized (Segment B/C)	2026	3029
Randomized and exposed	2016	3023
Re- randomized (Segment D)	648	1024
Re- randomized and exposed [primary efficacy - Intent-to-treat (ITT) and safety]	644	1017
Completed study treatment period	359	532
Completed study period	339	506
Pharmacokinetics		
Segment B/C	1484	2228

Diagnosis and criteria for inclusion:

Male or female patients ≥18 years of age who were smoking at least 10 cigarettes/day (on average) in the 2 months preceding screening visit and who were motivated to quit smoking (motivation scale score ≥6 on a 10-point scale).

Investigational product: Rimonabant

Dose: 5 mg or 20 mg once daily (as capsules containing 5 mg or 20 mg rimonabant)

Administration: Oral administration in the morning

Reference therapy: Placebo

Dose: Not applicable

Administration: Oral administration in the morning

Duration of treatment: 52 weeks

Duration of observation: 104 weeks

Criteria for evaluation:

Efficacy:

Primary analysis

The primary efficacy criterion was time to smoking relapse from the point of re-randomization into Segment D (Week 10) through Week 32 of Segment D. Smoking relapse was defined as any 7 or more consecutive days of smoking (with smoking defined by the "even a puff" criterion) or any 2 consecutive days of smoking 5 or more cigarettes per day (with smoking defined by the "even a puff" criterion).

The secondary efficacy criteria included other parameters related to abstinence (4-week prolonged abstinence, continuous abstinence, weekly point prevalence abstinence, and carbonmonoxyde), body weight, craving, lipid parameters, cluster of cardiovascular risk factors, Framingham score, QOL, and International Union Against Tuberculosis and Lung Disease (IUATLD) bronchial symptoms questionnaire at Weeks 32 and 52.

Secondary analysis, same as primary analysis but at end of Segment E (52 weeks)

During the post-treatment follow-up period (Segment F), non-relapse rate at Week 102, point prevalence abstinence, continuous abstinence, relative changes in body weight (non-obese patients and all patients without relapse to smoking at Week 102), craving, QOL and International Union Against Tuberculosis and Lung Disease (IUATLD) bronchial symptoms questionnaire were assessed.

Pharmacokinetics:
Rimonabant plasma concentrations were assessed both prior to administration of the investigational product (C_{trough}) at Weeks 10, 32, 52, and 58 and concurrently with electrocardiogram (ECG), approximately 2 hours after administration of the investigational product (C_{2h}) at Weeks 10, 32, and 52 using a validated liquid chromatography tandem mass spectrometry method with a limit of quantification of 5 ng/mL.

Pharmacokinetic/pharmacodynamic relationship:
The relationships between pharmacodynamic responses (primary and secondary efficacy variables and ECG data) and plasma concentrations were explored.

Safety:
Spontaneously reported adverse events (AEs), vital signs, physical findings, ECG, standard clinical laboratory values, and depression subscale scores from the Hospital Anxiety and Depression (HAD) scale were assessed. In addition, vital signs, AEs including all new serious adverse events (SAEs) were reported during Segment F, plus any non-SAEs which were ongoing from Segment E. Treatment emergent adverse events (TEAEs) were defined as events occurring after the first dose intake of the investigational product, up to and including 5 half-lives (75 days) after the last dose of investigational product in Segment D.

Statistical methods:

The primary efficacy endpoint was analyzed using a Kaplan-Meier time to event analysis. Time to smoking relapse was compared using a Log-rank test. Within each stratum, each rimonabant group was compared to placebo. Secondary efficacy endpoints were analyzed using Fisher's exact tests (for binary variables), Student's tests on least squares means (LS means) based on analysis of covariance (ANCOVA) (for quantitative variables), and Log-rank tests. For each rimonabant stratum, the primary efficacy population (ITT population, for the primary efficacy analysis) was defined as all re-randomized and exposed patients.

Plasma concentrations of rimonabant were summarized using descriptive statistics and relationships between pharmacodynamic responses and plasma concentrations were explored using graphical and regression methods.

Safety data were summarized by treatment group using descriptive statistics. Potentially clinically significant abnormalities in clinical laboratory test results, vital signs, and ECGs were flagged and analyzed.

Summary:

Baseline characteristics:

A total of 648 (32.1%) patients from the rimonabant 5 mg stratum and 1024 (33.9%) from the rimonabant 20 mg stratum were re randomized and entered Segment D. In each stratum, the rates of permanent treatment discontinuation observed during the maintenance period (Segment D up to and including Week 32) were similar between each rimonabant dose group and its corresponding placebo group.

In each stratum, demographic characteristics as well as medical and smoking histories were similar between each rimonabant treatment group and its corresponding placebo group. In the 5 mg group, 48.3% were male with a mean ± standard deviation (SD) age of 44.9 ± 11.1 years, body mass index (BMI) of 28.2 ± 5.8 kg/m^2, duration of regular smoking of 26.3 ± 11.4 years, and a total score on the Fagerström Test for Nicotine Dependence of 4.9 ± 2.1. In the 20 mg group, 49.9% were male with a mean ± SD age of 44.1 ± 11.1 years, BMI of 28.2 ± 5.6 kg/m^2, duration of regular smoking of 25.1 ± 11.2 years, and total score on the Fagerström Test for Nicotine Dependence of 5.1 ± 2.1. In each stratum, the rates of permanent treatment discontinuation observed during the maintenance period (Segment D up to and including Week 32) were similar between each rimonabant dose group and its corresponding placebo group.

A total of 359 (55.7%) patients from the rimonabant 5 mg stratum and 532 (52.3%) patients from the rimonabant 20 mg stratum completed the study treatment period. In the rimonabant 5 mg stratum, 382 patients (59.3%) entered Segment F and 339 patients (52.6%) completed the study. In the rimonabant 20 mg stratum, 571 patients (56.1%) entered Segment F and 506 patients (49.8%) completed the study (up to Week 102).

Efficacy results:

At Week 32, patients treated with 20 mg rimonabant and who continued 20 mg rimonabant (20mg/20 mg) and patients who were first treated with 20 mg rimonabant and then switched to 5 mg rimonabant (20 mg/5mg) showed statistically significant reduced smoking relapse rates compared to patient treated with 20 mg rimonabant and then switched to placebo (20 mg/plb) with p=0.011 and p=0.009, respectively. In the 20 mg/20 mg and 20 mg/5 mg treatment groups statistically significant results were also obtained for prolonged abstinence rates with p=0.001 and p=0.005, continuous abstinence rates with p=0.001 and p=0.005, and point prevalence abstinence rates with p=0.003 and p=0.002, respectively compared to the 20 mg/plb group. In addition, non-obese 20 mg/20 mg patients showed significantly less post-cessation weight gain compared to 20 mg/plb patients (p<0.001) while the 20 mg/5 mg patients did not show any effect on body weight. This effect of 20 mg rimonabant on the prevention of body weight gain was also observed in the 20 mg/20 mg ITT population (p<0.001) but not in the 20 mg/5 mg ITT population. In the population of successful quitters with rimonabant 20 mg, there was no evidence of an effect of rimonabant on craving.

In the 5 mg stratum, no effect on smoking relapse was demonstrated by the rimonabant 5 mg dose compared to patients switched to placebo.

At Week 52, the beneficial effect of rimonabant on smoking cessation continued. Patients treated with 20 mg/20 mg and 20 mg/5 mg showed statistically significant reduced smoking relapse rates compared to 20 mg/plb treated patient with p=0.005 and p=0.005, respectively. Likewise, in the 20 mg/20 mg and 20 mg/5 mg treatment groups statistically significant results were obtained for prolonged abstinence rates with p=0.001 and p=0.002, continuous abstinence rates with p=0.002 and p=0.003, and point prevalence abstinence rates with p=0.001 and p=0.002, respectively compared to the 20 mg/plb group.

Patients in the 20 mg/20 mg group experienced significantly less post-cessation weight gain (p=0.001) than 20 mg/5 mg or 20 mg/plb patients. Similar results were obtained in the ITT population with significantly less post-cessation weight gain (p<0.001) in patients in the 20 mg/20 mg group compared to patients in the 20 mg/5 mg or 20 mg/plb groups. No statistically significant differences between treatment groups were found for post-cessation weight gain in non-obese patients.

In the ITT population, patients in the 20 mg/20 mg group showed a statistically significant decrease in triglycerides (p=0.017) and a statistically significant increase in fasting high density lipoprotein cholesterol (p=0.0002) compared with 20 mg/5 mg or 20 mg/plb patients.

At Week 102, patients treated with 20 mg/20 mg or 20 mg/5 mg rimonabant had a significantly reduced smoking relapse than patients who received 20 mg/plb (ITT population, p=0.005 and p=0.018, respectively). In the rimonabant 5 mg stratum, no effect on smoking relapse was demonstrated by the rimonabant 5 mg dose compared to placebo. Weekly point prevalence abstinence rates and continuous abstinence rates were higher in the rimonabant 20 mg and 5 mg-treated patients compared with placebo-treated patients. In non-obese patients without relapse, and all patients (obese and non obese), the post-cessation weight gain was numerically lower in patients who had previously received exclusively rimonabant 20 mg, compared with the other 2 groups. There was no evidence of an effect of rimonabant on craving, QOL or IUATLD bronchial symptoms.

Pharmacokinetics:
At Week 10, doses of 5 and 20 mg/day rimonabant led to a mean ± SD C_{trough} of 36.7 ± 21.4 and 125 ± 69.3 ng/mL, respectively, and to a mean ± SD C_{2h} of 68.7 ± 36.5 and 214 ± 97.1 ng/mL, respectively.

At Week 52, doses of 5 and 20 mg/day rimonabant led to a mean ± SD C_{trough} of 32.4 ± 24.9 and 105 ± 76.8 ng/mL, and a mean ± SD C_{2h} of 63.7± 31.1 and 188 ± 87.6 ng/mL, respectively.

Pharmacokinetic/pharmacodynamic relationship:
At Week 32, prespecified analysis of rimonabant concentration relationship with efficacy endpoints showed a more marked effect on body weight change with increased plasma concentrations.

Results of the prespecified analysis of rimonabant concentration relationship with efficacy endpoints were consistent with the results of the previous efficacy analyses, showing a more marked effect on some endpoints (body weight change) with increased plasma concentrations.

Safety results:

Up to Week 32, overall, treatment-emergent adverse events (TEAEs) were frequently reported, slightly more in patients in the 20 mg/20 mg group compared to the 20 mg/5 mg and 20 mg/plb groups. The TEAEs reported most commonly (≥10%) in any treatment group of the 20 mg stratum were infections and infestations, psychiatric disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, and injury, poisoning and procedural complications. Individual TEAEs reported in ≥5% of patients in any group and more frequently with rimonabant, compared with placebo, were nasopharyngitis and headache. The rates of treatment discontinuation due to AE were slightly higher in the 20 mg/20 mg group compared to the 2 other groups. The rates of serious AEs were low and similar between groups. There was no evidence of events related to withdrawal from rimonabant.

Up to Week 52, TEAEs were slightly more frequent in the 20 mg/20 mg group compared to the 20 mg/5 mg and 20 mg/plb groups. The most frequently reported TEAEs in the 20 mg stratum were infections and infestations; psychiatric disorders; musculoskeletal and connective tissue disorders; gastrointestinal disorders; nervous system disorders; respiratory, thoracic and mediastinal disorders; and injury, poisoning and procedural complications. Individual TEAEs reported in ≥5% of patients in any group and more frequently with rimonabant, compared to placebo, were nasopharyngitis, influenza, headache, and back pain. The rates of treatment discontinuation due to AE were slightly higher in the 20 mg/20 mg group compared to the 2 other groups and the rates of serious AEs were low and similar between groups. No particular safety concerns were found with regard to clinical laboratory parameters, vital signs, or ECG parameters.

Up to Week 102, no fatal serious AEs were reported. The incidence of new and post-treatment serious AEs and AEs was low. Within the 20 mg stratum, 2 patients each reported serious AEs of syncope and coronary artery disease. No other post-treatment serious AE was reported by more than 1 patient and no post-treatment events raised any clinical concerns. A few new TEAEs (<5% in any treatment group) were collected for the segments B/C and D. The majority of these TEAEs were reported by a single patient within the 20 mg stratum and included musculoskeletal and connective tissue disorders, psychiatric disorders and infections and infestations. During Segment F a few new and minor TEAEs were reported that did not change the safety profile previously reported in the other segments.

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