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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00459004
Drug substance(s):	rimonabant (SR141716)	**Study Code:**	DRI5747
		Date:	31 May 2007

Title of the study:	A Dose-response Relationship Study of SR141716 in Obese Patients.
Coordinating Investigator:	Professor Kohji SHIRAI, M.D, Department of Internal Medicine, Toho University Sakura Medical Center, Japan.
Study centers:	73 active centers located in Japan
Publications:	Not applicable
Study period: Date first patient enrolled: 07 October 2004 Date last patient completed: 27 April 2006	**Phase of development:** Phase 2 (dose-ranging)
Objectives: Primary: Secondary:	• To verify the dose-response relationship of SR141716 on body weight change. • To compare the effect of 3 doses of SR141716 to placebo, on body weight loss and on secondary criteria associated with comorbidities; • To evaluate the safety of SR141716; • To evaluate the pharmacokinetics (PK) of SR141716.
Methodology:	Multicenter, randomized, double-blind, placebo-controlled, parallel group, 3 fixed-dose regimens [SR141716 5 mg, 10 mg, and 20 mg once daily (OD)], 24-week study with 4-week follow-up. Following a 4-week screening period and a 4-week placebo observation period, patients were randomized to 1 of the 4 treatment groups : placebo, SR141716 5 mg, 10 mg or 20 mg for 24 weeks of double-blind treatment using a randomization ratio of 1:1:1:1. At the end of the double-blind treatment period, patients entered a follow-up period of 4 weeks. During the placebo observation, treatment, and follow-up periods, a mild hypocaloric diet was adapted to each patient. During the double-blind period, patients were seen every 4 weeks until Week 24.
Number of patients:	Planned**:** 432 Randomized**:** 527 Treated**:** 526

Diagnosis and criteria for inclusion:	Male or female outpatients aged between 20 and 70 years, with a body mass index (BMI) ≥25 kg/m², a visceral fat area (VFA) ≥100 cm², a diet therapy for more than 8 weeks before start of the placebo observation period, a stable body weight (variation <= 3 kg within 8 weeks before start of observation period), and at least 2 of the following comorbidities: • Impaired glucose tolerance (IGT) or type 2 diabetes; • Dyslipidemia [hypertriglyceridemia and/or low high density lipoprotein-cholesterol (HDL-C)]; • Hypertension.	
Investigational product: Dose: Administration:	SR141716 (capsules of 5 mg, 10 mg, and 20 mg) 5, 10, or 20 mg OD for 24 weeks (6 months) oral	
Duration of treatment:	24 weeks	**Duration of observation:** approximately 36 weeks, including 4-week screening, 4-week placebo observation, 24 week- treatment, and 4-week follow up.
Reference therapy: Dose: Administration:	Placebo (matched capsules) Not applicable Oral for 4 weeks in the placebo observation period, and for 24 weeks in the treatment period	
Criteria for evaluation:		
Efficacy:	***Primary efficacy criterion:*** Absolute change in body weight from baseline to Week 24 (or to last available visit). Secondary analysis on the primary efficacy criterion: percentage of responders at 5% (body weight loss ≥5% from baseline) and 10% (body weight loss ≥10% from baseline) at Week 24. ***Main secondary efficacy criteria:*** • waist circumference; • VFA; • BMI; • triglycerides (TG), HDL-C; • glycosylated hemoglobin (HbA_{1c}); fasting plasma glucose (FPG); plasma glucose 2-hour post-load [oral glucose tolerance test (OGTT)] for patients having IGT as one of comorbidities; • blood pressure (BP).	
Safety:	• Recording and monitoring of adverse events (AEs) throughout the study; • Physical examination; • Clinical laboratory tests (hematology, serum chemistry, urinalysis); • Vital signs [heart rate (HR) and BP] measurements; • 12-lead electrocardiograms (ECGs): standard ECG parameters with a centralized manual review.	
Pharmacokinetics:	SR141716 plasma trough concentrations	
Pharmacokinetic/ Pharmacodynamic relationships:	Relationship between pharmacodynamic responses (change in body weight, TG, HDL-C, HbA_{1c}, and ECG variables) and SR141716 plasma trough concentrations	

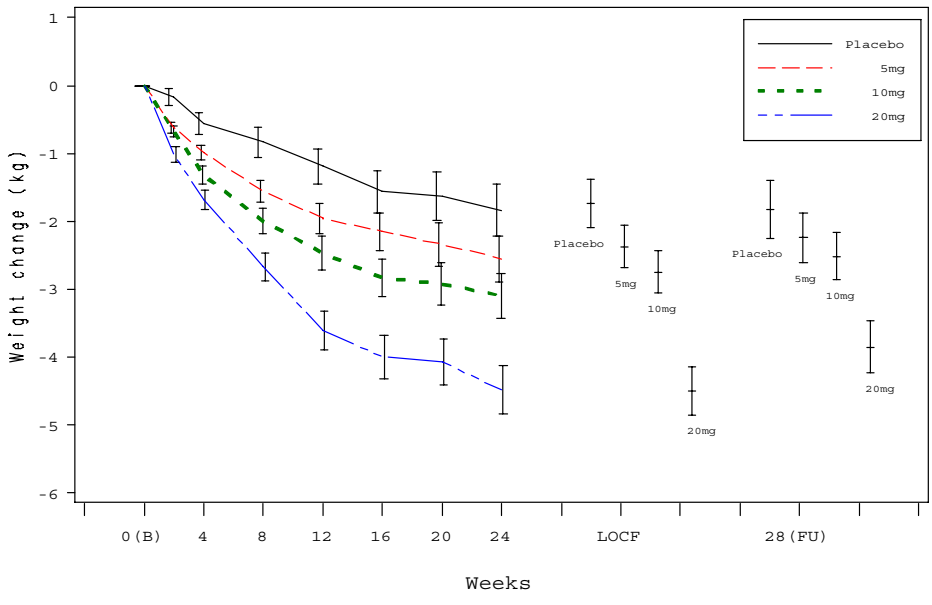
Pharmacokinetic sampling times and bioanalytical methods:	***Sampling times:*** Blood samples for SR141716 plasma assays were drawn prior to dosing at Weeks 2, 4, 8, 12, 16, 20, 24, and 28 (follow-up visit), as well as at the time of discontinuation, if any. ***Bioanalytical methods***: Plasma concentrations of SR141716 were quantified using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 5 ng/mL.
Statistical methods:	Efficacy analyses were performed in the intent to treat (ITT) population on last observation carried forward (LOCF). Completers at Week 24 and per protocol (PP) populations were used as complementary analyses. Differences versus baseline were expressed as least square mean (LS mean) ± standard error of the LS mean (SEM). Differences versus placebo were expressed in LS mean ± SEM. The safety population consisted of exposed population, i.e., all randomized patients who were exposed to at least 1 dose of double–blind investigational product (IP).
Efficacy:	Primary efficacy analyses were performed in the ITT population on the LOCF. A contrast test of linear trend using contrast coefficient [7, 3, -1, -9] within the framework of analysis of covariance (ANCOVA) model was performed at two-sided 5% significant level. The model included absolute change in body weight from baseline as response, treatment as a fixed effect and baseline body weight as a covariate. If contrast test for dose-response relationship was significant, each dose of SR141716 was compared to placebo in the order of descending dose using appropriate contrast within the model at two-sided 5% significant level, until non-significance was observed at any dose level, according to closed testing procedure for keeping global type I error. Placebo-adjusted LS means and confidence intervals (CIs) were also provided. The same statistical methodology was applied for secondary efficacy quantitative parameters.
Safety:	Safety and tolerance data were summarized by treatment group using descriptive statistics. No statistical tests were planned to be performed. All AEs were coded using the Medical Dictionary for Regulatory Activities in Japanese version (MedDRA/J Version 9.0). Treatment-emergent adverse events (TEAEs) were defined as AEs that occurred or worsened or became serious during double-blind study treatment exposure or within 45 days following the last double-blind IP intake. Treatment-emergent AEs, serious adverse events (SAEs), and AEs leading to study treatment discontinuation were analyzed by system organ class (SOC) and preferred term (PT). Descriptive statistics over time were provided for clinical laboratory, hemodynamic and ECG parameters. Abnormalities in hematology and biochemistry parameters, vital signs, and ECG parameters were assessed using potentially clinically significant abnormality (PCSA) criteria.
Pharmacokinetics:	SR141716 plasma concentrations were summarized using descriptive statistics. The occurrence of C_{trough} steady state for SR141716 was assessed by statistical model.
Pharmacokinetic/ pharmacodynamic relationships	The relationship between pharmacodynamic responses [change in body weight, TG, HDL-C, $HbA_{1C,}$ ECG parameters] and SR141716 plasma concentrations was explored.

Summary:

Study population: A total of 527 patients were randomized in the study, and 526 of them were exposed to placebo (131 patients), SR141716 5 mg (133 patients), SR141716 10 mg (130 patients), or SR141716 20 mg (132 patients). One patient was exposed to study treatment (SR141716 10 mg) without postbaseline efficacy assessment leading to 525 patients in the ITT population. Four hundred and fifty-five (455) patients (86.3%) completed the 24-week study treatment.
Of the 526 randomized and exposed patients, 381 (72.4%) were male and 145 (27.6%) female, the mean standard deviation (SD) age was 46.9 (10.1) years with a mean (SD) baseline BMI of 31.2 (4.6) kg/m², a mean (SD) baseline body weight of 86.6 (15.7) kg, a mean (SD) baseline waist circumference of 101.7 (10.3) cm and a mean (SD) VFA of 179.7 (57.2) cm² .

Efficacy results: A clear dose effect relationship was observed for body weight loss in the SR141716 groups (trend test p <0.0001). SR141716 doses of 10 mg and 20 mg showed significant differences as compared to placebo, and LS mean differences from placebo were –1.0 kg (p = 0.0346) in the 10 mg group and –2.8 kg (p <0.0001) in the 20 mg group. SR141716 20 mg induced a greater reduction of body weight.
Waist circumference and BMI decreases followed the same pattern as body weight loss with also clear dose effect relationship (trend test p <0.0001 for both parameters) and a significant greater decrease with SR141716 20 mg (p=0.0001 and p<0.0001, respectively). No difference was seen between the 5 mg dose and placebo for all these parameters.

Body weight change (kg) by visit and LOCF at Week 24 (Mean ± SE) - ITT population



PGM=SR141716/DRI5747/pg/rep/eff/a0410eg.sas; OUT=SR141716/ZZDRI5747/out/outb/a0410eg2.emf(29NOV2006-16:23)

Efficacy results (Continued):

Visceral fat was also reduced in a dose related manner with a significant greater reduction in the SR141716 20 mg group ($p<0.0001$ versus placebo).

Treatment with SR141716 20 mg resulted in a significant increase in HDL-C levels (LS mean difference from placebo of 10.6%, $p <0.0001$) and a significant decrease in triglyceride levels (LS mean difference from placebo of -12.8%, $p=0.0361$) compared with placebo. SR141716 10 mg showed significant differences in HDL-C (5.4 %, $p = 0.0049$) compared with placebo, but not for TG. No difference was seen between SR141716 5 mg and placebo.

For glycemic control parameters, in the SR141716 20 mg group where the baseline HbA_{1c} value (5.93%) was low, a significant decrease in HbA_{1c} by 0.23% from baseline was observed compared with a decrease of 0.02% in the placebo group at week 24 (difference of 0.20%, $p = 0.0096$). SR141716 5 mg and 10 mg did not show difference with placebo.

The improvement in HbA_{1c} was associated with decreases in fasting plasma glucose and fasting insulin, with a greater decrease of fasting insulin in the 20 mg group. Insulin resistance as assessed by homeostasis model assessment (HOMA) was also improved, this improvement was more pronounced with SR141716 20 mg.

Adiponectin increased in a dose related manner with a significant greater increase in the SR141716 20 mg group than in the placebo group ($p <0.0001$). No difference was observed between SR141716 5 mg and placebo, as well as between SR141716 10 mg and placebo.

Safety results:

The numbers and percentages of randomized and exposed patients with at least 1 TEAE during the study are presented in the following table.

Overall summary of the number (%) of patients experiencing at least 1 TEAE - Randomized and exposed patients

		SR141716			
	Placebo (N=131)	5 mg (N=133)	10 mg (N=130)	20 mg (N=132)	Total (N=395)
Patients with any TEAE	99 (75.6%)	107 (80.5%)	98 (75.4%)	100 (75.8%)	305 (77.2%)
Patients with any serious TEAE	5 (3.8%)	1 (0.8%)	4 (3.1%)	4 (3.0%)	9 (2.3%)
Patients with any TEAE leading to death	0	0	0	0	0
Patients with any TEAE leading to study discontinuation	10 (7.6%)	7 (5.3%)	12 (9.2%)	6 (4.5%)	25 (6.3%)

The percentages of patients with at least 1 TEAE were similar across the treatment groups with no dose effect. In the SR141716 20 mg group, the TEAEs reported in ≥2% of the patients and with an incidence >1% compared to placebo, were upper respiratory tract inflammation, nausea, increased CPK, hypoesthesia, laryngopharyngitis, influenza, hemorrhoids, musculoskeletal stiffness, fatigue, and asthenopia. A dose effect was only observed for hypoesthesia, which was reported with an incidence of 0.8 % and 3.8% in the SR141716 10 mg and 20 mg, respectively, versus 0% in the placebo and SR141716 5 mg groups. The overall profile of TEAEs was comparable in the three SR141716 and placebo groups. Most of the TEAEs were of mild or moderate intensity, and resolved without corrective therapy.

Safety results (Continued):	The percentages of patients with at least 1 SAE were low in all groups with no dose effect. None of the SAEs reported in the SR141716 groups was considered to be possibly related to study treatment by the investigators. No deaths were reported during the study. There was no dose effect in the percentage of patients who permanently discontinued the study treatment due to TEAEs, with a lower percentage in the SR141716 20 mg group. The most frequent TEAEs leading to study discontinuation in the SR141716 groups were liver function abnormalities (including abnormal liver function test, increased ALT, increased AST, and hepatobiliary disorders), with a comparable rate in the placebo and SR141716 5 mg and 10 mg groups, and nervous system disorders, reported with a slightly higher incidence than in the placebo group. No particular signal was detected through the analyses of laboratory, vital signs, and ECG parameters.
Pharmacokinetic results:	SR141716 plasma concentrations reached steady-state at a median time of 35 days with the doses of 5, 10 and 20 mg/day leading to mean (SD) trough concentrations of 53.6 (29.8) ng/mL, 84.9 (57.3) ng/mL, and 145 (84.7) ng/mL, respectively, at Week 24.
Pharmacokinetic/ pharmacodynamic results:	Relative to baseline, body weight decreased and HDL-C increased with increase in plasma concentrations of SR141716.
Date of full report:	06 February 2007