SYNOPSIS

Title of the study:	Randomized, multicenter, double-blind, placebo-controlled, two-arm parallel group trial of rimonabant 20-mg od, for inhibition of atherosclerosis progression assessed by IVUS (IntraVascular UltraSounds), in overweight patients with clustering risk factors		
Coordinating investigator:	[redacted]		
Study centers:	126 study centers screened patients and 112 active study centers in the USA, Canada, Belgium, France, Italy, Netherlands, Poland, Spain, and Australia randomized patients		
Publications (reference):	Nissen E, Nicholls SJ, Wolski K, Rodés-Cabau J, Cannon CP, et al. Effect of rimonabant on progression of atheroscloerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA Express 2008; 299(13):1547-1560.		
Study period:	Date first patient enrolled/first patient randomized: 22 December 2004/14 January 2005 Date last patient completed: 19 October 2007		
Phase of development:	3		
Objectives:			
Primary	To evaluate the effect of rimonabant 20 mg once daily in comparison with placebo, on the quantitative progression of coronary atherosclerosis as assessed by intravascular ultrasound (IVUS)		
Secondary	To evaluate the safety and tolerability of the above rimonabant regimen in the study population		
Methodology:	Phase 3, prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, 2-arm parallel group trial (rimonabant 20 mg once daily versus placebo). Three-stage screening process including, in succession, a screening visit, baseline coronary angiography/IVUS, and validation of the latter by IVUS core laboratory. Patients who complied with all inclusion and exclusion criteria were randomized to 1 of the 2 treatment groups less than 2 weeks after a baseline IVUS. At inclusion, patients were recommended to comply with a mild hypocaloric diet and smoking cessation (if smokers) for the entire study duration. In addition, the Investigators were recommended to treat their patients as appropriate for their risk factors by initiating and/or optimizing the prescription of background therapies at the early stage of the observation, and keeping those medications stable as much as possible after 8 weeks postrandomization up to follow-up completion. Patients were treated with the study drug and followed up during the 18- to 20-month treatment period. The final IVUS assessment (primary endpoint) occurred at the end of the 18- to 20-month treatment period.		
Number of patients:	Planned: 800	Randomized: 839	Treated: 838
Evaluated:	Efficacy: 676	Safety: 838	Pharmacokinetics: NA
Diagnosis and criteria for inclusion:	Patients >18 years of age with an indication for coronary angiography and with abdominal obesity (waist circumference >88 cm in women or >102 cm in men), and at least 1 of the 2 following additional risk factors: • Metabolic syndrome as defined by the presence of at least 2 of the following additional risk factors: – Triglyceride level ≥150 mg/dL (1.69 mmol/L) – HDL cholesterol <40 mg/dL (1.03 mmol/L) for men or 50 mg/dL (1.28 mmol/L) for women – Fasting glucose ≥110 mg/dL (6.1 mmol/L) – High blood pressure (≥140 mmHg systolic and/or ≥90 mmHg diastolic) at screening visit, or		

	current treatment by antihypertensive medication • Currently smoking (>10 cigarettes/day) and willing to stop In addition, angiographic evidence of coronary heart disease as defined by at least 1 lesion in a native coronary artery that has ≥20% reduction in lumen diameter by angiographic visual estimation and the presence of at least one coronary artery complying with the definition of "target vessel" for IVUS assessment.
Investigational product	SR141716 (rimonabant)
Dose:	20 mg tablet of rimonabant, once a day
Administration:	Oral
Batch numbers:	[redacted]
Duration of treatment:	18 to 20 months
Duration of observation:	21 months (planned)
Reference therapy:	Placebo
Dose:	Matched rimonabant tablet
Administration:	Oral
Batch numbers:	[redacted]
Criteria for evaluation:	
Efficacy:	**Primary endpoint**: The primary efficacy endpoint was the absolute change in percentage atheroma volume (PAV) between baseline and final intravascular ultrasounds (IVUS) (ie, at Month 18 visit or, if not available, at least 320 days after randomization). **Secondary endpoint**: The secondary efficacy endpoint was the nominal change in normalized total atheroma volume (nTAV) of the target coronary artery between baseline and final IVUS. Other efficacy endpoints: • Time from randomization to first occurrence of stroke, myocardial infarction, or cardiovascular death • Time from randomization to first occurrence of stroke, myocardial infarction, cardiovascular death, hospitalization for revascularization procedure, hospitalization for unstable angina, or hospitalization for transient ischemic attack • Absolute change from baseline in body weight, waist circumference, systolic and diastolic blood pressure, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, fasting glucose, and glycosylated hemoglobin A1c (HbA_{1c}) • Change from baseline in smoking status for patients who were current smokers at baseline
Safety:	Treatment-emergent adverse events, clinical laboratory evaluations (hepatic function, renal function, metabolism, white blood cells, red blood cells, and platelet count), vital signs, and 12-lead electrocardiogram (ECG). Particular attention was paid to neuropsychiatric events, which were specifically documented via a complementary data query process.
Statistical methods:	For all efficacy and safety parameters, patients were analyzed according to the allocated treatment by the interactive voice response system (IVRS) at the time of randomization.
Efficacy	Analysis populations: • **All randomized population**: All randomized patients, irrespective of whether the patient actually received the study drug or complied with the study protocol. • **Intent-to-treat population**: All randomized patients having reached a final IVUS • **Per-protocol population**: All randomized patients having reached a final IVUS at Month 18 (at least 480 days after randomization) under study drug at that time (on study drug or still exposed to

	study drug – date of final IVUS – actual date of last study drug ≤ 75 days), fulfilling all inclusion criteria and having never received a study treatment different from the one allocated at the randomization stage**.** Analyses: The primary analysis was a covariance analysis done on the change in PAV including study treatment and baseline PAV value as fixed effect. This analysis was performed on the intent-to-treat population. The same analysis was performed on the per-protocol population; the normality was also explored and, if clearly rejected, a nonparametric approach was to be used. The analysis of the secondary endpoint was done on the intent-to-treat population. The statistical analysis was the same as the one described for the primary analysis of the primary endpoint. This analysis was done using a hierarchical procedure: change in nTAV between baseline and final IVUS being tested only if the primary analysis of the primary endpoint was significant, without adjustment at a significance level of 5%. • Time to event parameters were analyzed in the all randomized population. The time from randomization to each defined clustered endpoint was compared between the 2 treatment groups using a 2-sided log-rank asymptotic test. Cumulative incidence functions in each treatment group were calculated and plotted using a nonparametric Kaplan-Meier estimate. Hazard ratio with 95% confidence interval was estimated using the Cox model with treatment group as the only factor. • In order to further investigate the relationship between indicators of atherosclerosis progression observed by IVUS (primary and secondary efficacy endpoints) and rimonabant-induced effects on quantitative parameters (absolute change from baseline in body weight, waist circumference, systolic blood pressure, diastolic blood pressure, HDL-C, LDL-C, triglycerides, fasting glucose, and HbA_{1c}), a covariance analysis was done on the intent-to-treat population for each of these parameters and each of the 2 indicators of atherosclerosis progression.
Safety	All safety analyses were performed on the exposed population (ie, all patients receiving at least 1 study drug administration), considering all assessments which occurred during the on-treatment period (ie, between the first study drug intake and the last study drug intake plus 75 days, both boundaries included). The frequency of patients having experienced at least 1 treatment-emergent adverse event (TEAE), noncardiovascular TEAE resulting in death, a serious TEAE, and a TEAE leading to discontinuation of treatment is summarized by treatment group according to MedDRA (Medical Dictionary for Regulatory Activities, Version 10.1) terminology. Clinical laboratory data, vital signs, and ECG parameters, and their changes from baseline were summarized at each protocol time point. The number and percentage of patients presenting at least 1 postbaseline potentially clinically significant abnormality (PCSA) in laboratory data, vital signs, and ECG parameters were summarized by treatment group.
Summary:	
Efficacy results:	A total of 422 patients in the rimonabant 20 mg group and 416 patients in the placebo group were exposed to at least 1 dose of study drug. The majority of patients completed the study drug period. The 2 treatment groups were well balanced for demographic and baseline characteristics, including cardiovascular history, metabolic syndrome risk factors, and the use of metabolic and psychotropic medications taken at baseline. The majority of patients (over 80%) in both treatment groups had a history of hypertension and hypercholesterolemia, and used acetyl salicylic acid at baseline. Over 80% of patients in each treatment group were taking statins at baseline and continued to use statins during the study. Around 20% of patients in each treatment group were taking antidepressant medications (including serotonin reuptake inhibitor) at baseline. The progression of PAV observed in the placebo group was slightly higher than that in the rimonabant 20 mg group (least-square mean difference 0.26%, 95% confidence interval of -0.15 to 0.66). However the difference between treatment groups of this primary efficacy endpoint was not statistically significant (p = 0.2195). A regression in the nTAV (the secondary efficacy endpoint) was observed in the rimonabant group

	(least-square mean difference between the placebo group and the rimonabant 20 mg group 3.0 mm^3, 95% confidence interval of 0.3 to 5.8), suggesting a clinically relevant effect with rimonabant. The nominal p-value for the difference between treatment groups of this secondary efficacy endpoint was 0.0280. Analysis of the time to first occurrence of stroke, myocardial infarction, or cardiovascular death indicated a higher cumulative incidence in the rimonabant 20 mg group compared with the placebo group; however the difference between the treatment groups was not statistically significant. Analysis of the time to first occurrence of stroke, myocardial infarction, cardiovascular death, or hospitalization for unstable angina, transient ischemic attack, or revascularization procedure, indicated a higher cumulative incidence in the placebo group compared with the rimonabant 20 mg group; however the difference between the treatment groups was not statistically significant. Additional analyses confirmed that rimonabant had a statistically significant effect on body weight, waist circumference, HDL-C, triglycerides, and glycosylated hemoglobin, when compared with placebo. This is consistent with other rimonabant trials. Rimonabant did not have a significant effect on systolic blood pressure, diastolic blood pressure, or LDL-C, when compared with placebo. The covariance analyses which were performed on the intent-to-treat population, in order to investigate the relationship between indicators of atherosclerosis progression, suggested that there was a relationship between the change in HDL-C and both the primary endpoint (PAV) and the secondary endpoint (nTAV). To a lesser extent, there was a relationship between the change in waist circumference and both PAV and nTAV. In exploratory multivariate analyses, baseline LDL-C value, the number of metabolic risk factors, the level of triglycerides in class, and the use of statins at baseline were identified as baseline predictive factors of the progression of PAV. Moreover, there appeared to be an interaction between the treatment and the use of statins at baseline and an interaction between the treatment group and the level of triglycerides. In the subgroup of patients not using statins at baseline and the subgroup of patients with a level of baseline triglycerides ≥ median (1.58 mmol/L), rimonabant had a significant change effect on PAV.
Safety results:	The safety population was comprised of 838 patients (all treated patient population). Of note, patients with a severe psychological condition were excluded from the study population, but the protocol allowed concomitant use of antidepressant medications. The incidence of patients experiencing TEAEs was higher in the rimonabant 20 mg group (81.5%) when compared with the placebo group (74.0%). The system organ classes with events more frequently reported in the rimonabant 20 mg group when compared with the placebo group, were the psychiatric disorders (43.4% versus 28.4%), and gastrointestinal disorders (33.6% versus 17.8%). The most common TEAEs reported by ≥5% of patients in the rimonabant 20 mg group (and ≥ 1% over the placebo group) were anxiety (18.0% versus 11.8%), depression (16.8% versus 11.3%), nausea (14.9% versus 5.5%), dizziness (14.5% versus 12.7%), insomnia (12.3% versus 9.1%), fatigue (10.9% versus 6.0%), noncardiac chest pain (8.8% versus 5.0%), diarrhea (7.8% versus 3.4%), depressed mood (6.9% versus 4.8%), vomiting (5.5% versus 1.9%), and asthenia (5.2% versus 3.8%). There were 12 deaths reported in this study. Two deaths occurred during the screening period. Of the 10 deaths reported after randomization, 3 were of cardiovascular origin and occurred in the placebo group. A total of 7 deaths were of noncardiovascular origin, 5 in the placebo group and 2 in the rimonabant group. Serious TEAEs were more frequently reported in the rimonabant 20 mg group when compared with the placebo group (19.4% versus 15.9%). Serious TEAEs were generally reported by not more than 1 or 2 patients in either treatment group. The most common system organ classes with serious TEAEs reported with an incidence ≥2% in rimonabant 20 mg group (and ≥1% over the placebo group) were general disorders and administration site conditions (4.3% versus 2.4%), gastrointestinal disorders (4.0% versus 2.6%), musculoskeletal and connective tissue disorders (3.1% versus 1.4%), and psychiatric disorders (2.1% versus 1.2%). The number and percentage of patients who

	discontinued treatment due to an adverse event were higher in the rimonabant group when compared with the placebo group (17.5% versus 7.5%). The most frequent events, which resulted in permanent discontinuation in the rimonabant 20 mg group (compared with the placebo group) were depression (3.6% versus 1.2%), nausea (3.1% versus 0.2%), anxiety (3.1% versus 0.7%), insomnia (1.7% versus 0.2%), and dizziness (1.7% versus 0.2%). For laboratory parameters, PCSAs were generally very few and similar between the 2 treatment groups. Of note, fewer patients in the rimonabant 20 mg group had PCSAs for triglycerides, HbA1c, and blood glucose when compared with the placebo group.
Conclusions:	[redacted]
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