

The SERENADE Trial: Effects of Monotherapy with Rimonabant, the First Selective CB₁ Receptor Antagonist, on Glycemic Control, Body Weight and Lipid Profile in Drug-naïve Type 2 Diabetes

Julio Rosenstock MD¹, Priscilla Hollander MD², Soazig Chevalier MS³, Ali Iranmanesh MD⁴; for the SERENADE study group.

¹Dallas Diabetes and Endocrine Center, TX, USA; ²Baylor Endocrine Center, TX, USA; ³sanofi-aventis R&D, Antony, France; ⁴Salem Veterans Affairs Medical Center, VA, USA.

Correspondence:

Julio Rosenstock MD

Email: juliorosenstock@dallasdiabetes.com

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Objective – To assess the glucose-lowering efficacy and safety of rimonabant monotherapy in drug-naïve, type 2 diabetes (T2DM) patients.

Research design and methods – SERENADE was a 6-month, randomized, double-blind, placebo-controlled trial of rimonabant 20 mg/day in drug-naïve patients with T2DM (HbA_{1c} 7–10%). Primary endpoint was HbA_{1c} change from baseline; secondary endpoints included body weight, waist circumference and lipid profile changes.

Results – 281 patients were randomized, 278 were exposed to treatment, and 236 (84.9%) completed the study. Baseline HbA_{1c} (7.9%) was reduced by –0.8% with rimonabant versus –0.3% with placebo (Δ HbA_{1c} –0.51%; $P = 0.0002$), with a larger rimonabant effect in patients with baseline HbA_{1c} $\geq 8.5\%$ (Δ HbA_{1c} –1.25%; $P = 0.0009$). Weight loss from baseline was –6.7 kg with rimonabant versus –2.8 kg with placebo (Δ weight –3.8 kg; $P < 0.0001$). Rimonabant induced improvements from baseline in waist circumference (–6 vs. –2 cm; $P < 0.0001$), fasting plasma glucose (–0.9 vs. –0.1 mmol/L; $P = 0.0012$), triglycerides (–16.3% vs. +4.4%; $P = 0.0031$) and HDL-cholesterol (+10.1% vs. +3.2%; $P < 0.0001$). Adverse events of interest that occurred more frequently with rimonabant versus placebo: dizziness (10.9% vs. 2.1%), nausea (8.7% vs. 3.6%), anxiety (5.8% vs. 3.6%), depressed mood (5.8% vs. 0.7%) and paresthesia (2.9% vs. 1.4%).

Conclusions – Rimonabant monotherapy resulted in meaningful improvements in glycemic control, body weight and lipid profile in drug-naïve T2DM patients. Further ongoing studies will better establish the benefit:risk profile of rimonabant and define its place in T2DM management.

An increasing worldwide burden of type 2 diabetes (T2DM) is being driven by the obesity epidemic (1,2). Studies suggest that abdominal obesity may play an important role in the pathogenesis of multiple cardiometabolic risk factors present in T2DM, which contribute substantially to the increased cardiovascular risk in this population (3–5).

Comprehensive T2DM management involves glucose, lipid and blood pressure control, often requiring multiple pharmacotherapies plus lifestyle changes to achieve weight loss (6). However, weight loss is generally more difficult in T2DM patients and moreover, thiazolidinediones, sulfonylureas and insulin cause weight gain, whereas metformin and incretin-related therapies tend to be weight neutral or induce modest weight loss (7–11).

The endocannabinoid system regulates energy homeostasis, and lipid and glucose metabolism through G-protein-coupled cannabinoid (CB₁) receptors located in the brain, adipose tissue, liver, skeletal muscle and pancreas (12,13). CB₁ antagonism in these tissues directly modulates fat deposition in liver and adipose tissue, fatty acid synthesis, and glucose disposal (12,13), and may represent a potential drug target for T2DM (14).

Rimonabant, a selective CB₁ receptor antagonist, has been shown to reduce body weight and improve glycemic control in overweight/obese patients with T2DM sub-optimally controlled on metformin or sulfonylurea monotherapy (15). We report the results of SERENADE (Study Evaluating Rimonabant Efficacy in drug-NAïve DiabEtic patients), an exploratory study to assess the glucose-lowering efficacy and safety of rimonabant monotherapy in drug-naïve T2DM and the first trial to use HbA_{1c} as the primary endpoint.

RESEARCH DESIGN AND METHODS

Patients—This randomized, double-blind, parallel, placebo-controlled, multinational study recruited patients from 56 centers (March 22, 2005 – June 10, 2006). Eligible T2DM (16) patients were aged ≥ 18 years with duration >2 months but <3 years, and with HbA_{1c} $\geq 7\%$ and $\leq 10\%$. Prior use of oral antidiabetic agents was not permitted within 6 months of screening and only for ≤ 4 months in duration. Exclusion criteria included: weight loss >5 kg within previous 3 months; pregnancy or lactation; use of anti-obesity treatments within previous 3 months; changes to lipid-modifying treatments within previous 2 months; any clinically significant disorders (endocrine/metabolic/severe psychological disorders; presence/history of cancer; laboratory abnormalities). Patients with a history of depression were not excluded from this study.

The study protocol was approved by Institutional Review Boards/Independent Ethics Committees at each site to comply with the Declaration of Helsinki; all patients provided written informed consent.

Study design—Following a 1–2 week screening period with instructions not to change diet, patients were randomized to double-blind rimonabant 20 mg or matching placebo (1:1 ratio) for 6 months. Randomization was stratified according to HbA_{1c} at screening ($\geq 7\%$ to $<8.5\%$ or $\geq 8.5\%$ to $\leq 10\%$). All patients received American Diabetes Association dietary recommendations (6) by a dietician at baseline and reinforced at 3 and 6 month study visits. Overweight (body mass index [BMI] ≥ 27 – <30 kg/m²) or obese (BMI ≥ 30 kg/m²) patients were instructed to follow a 600-kcal/day caloric deficit. All patients were encouraged to increase physical activity.

The study primary endpoint was absolute change in HbA_{1c} from baseline to study end (month 6). Pre-specified secondary efficacy parameters, as in any antidiabetic

trial, included the proportion of patients achieving predefined glycemic targets ($HbA_{1c} < 6.5\%$ or $< 7\%$), and changes in fasting plasma glucose (FPG), body weight, waist circumference, high-density lipoprotein (HDL)-cholesterol, triglycerides, low-density lipoprotein (LDL) particle size, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), HOMA β -cell function (HOMA-BCF), adiponectin, leptin, ghrelin, blood pressure and urinary albumin/creatinine ratio (17).

Patients with $HbA_{1c} > 9\%$ at 3 months confirmed by a repeat measurement 1 month later could receive rescue medication at the investigator's discretion.

Measurements—Primary and secondary efficacy parameters were measured at screening and/or baseline and at 3 and 6 months post-randomization. Body weight and vital signs were measured at screening, baseline and monthly thereafter.

Blood samples for measurement of metabolic parameters were taken under fasting conditions and analyzed at a central laboratory (MDS Diagnostic Services, Mississauga, Ontario, Canada). HbA_{1c} was measured using ion-exchange high-pressure liquid chromatography with DCCT reference values.

Safety analyses were based on standard adverse event (AE) reporting. All AEs were coded using the global Medical Dictionary for Regulatory Activities (MedDRA, version 9.0). AEs were analyzed using MedDRA by system organ classification and the sub-category, preferred term. Unblinded safety data were evaluated in an ongoing manner by an independent Data Monitoring Committee. During each visit, investigators used a questionnaire of scripted neurological and psychiatric questions (see online Appendix A available at <http://care.diabetesjournals.org>). Any AE related to a depressive disorder or neurologic AE was captured by patients self-reporting

the event to the investigator and recorded in a standard AE/serious AE (SAE) form for each episode; a questionnaire was then completed and the AE/SAEs coded using MedDRA terminology (online Appendix A). Symptoms were only recorded when the diagnosis was unknown. Any AE/SAE reported within 75 days of the last study drug dose was included in the safety database. Hypoglycemia was defined as clinical symptoms consistent with hypoglycemia, with or without a confirmatory blood glucose measurement.

Statistical analysis—Sample size calculations were based on an assumed difference in HbA_{1c} of -0.8% between the rimonabant 20 mg and placebo groups at 6 months (SD for the change from baseline in HbA_{1c} of 1.6%). A sample size of 132 patients per group was estimated to provide 95% power to detect this treatment difference with a two-sided significance level of 0.05, assuming an overall study dropout rate of 20%. An intention-to-treat (ITT) analysis (primary analysis) was conducted using last observation carried forward (LOCF). The ITT population comprised all patients who received at least one dose of double-blind treatment and had at least one assessment post-randomization. All efficacy data obtained after the introduction of rescue medication were excluded from the analysis. The safety population included all patients randomized and exposed to treatment. Descriptive data for AEs were reported using numbers and percentage of patients; statistical analyses were not performed.

Statistical analyses were performed using SAS version 8.2. Continuous variables were measured using repeated measures analysis of covariance (ANCOVA), with treatment, country and randomization stratum as fixed effects, and baseline assessment as covariate. Categorical data were analyzed using a Cochran-Mantel-Haentzel test stratified on country and randomization

stratum. *P*-values were two-sided and unadjusted.

RESULTS

In total, 281 patients were randomized to rimonabant 20 mg (n=140) or placebo (n=141) (online Appendix Fig. 1). Two patients in the rimonabant group and one in the placebo group did not receive study treatment and were excluded from the efficacy set. The ITT efficacy population comprised 130 and 131 patients in the rimonabant and placebo groups, respectively. Of the 278 patients randomized and exposed to treatment, 236 patients (84.9%) completed the study: 80.4% and 89.3% in the rimonabant and placebo groups, respectively. Overall, 27 patients receiving rimonabant discontinued treatment (AEs [13]; patient request [8]; lost to follow-up [2]; poor compliance [1]; other reasons [3]) versus 15 patients receiving placebo (lack of efficacy [4]; lost to follow-up [4]; AEs [3]; patient request [3]; other reasons [1]). Rescue medication was required by four patients (2.9%) in the rimonabant group and 14 patients (10.0%) in the placebo group.

Treatment groups were well balanced for demographic and baseline disease characteristics (Table 1). Mean baseline HbA_{1c} was 7.9% and most participants were overweight or obese (90% had BMI >27 kg/m²). There was a high prevalence of cardiometabolic risk factors including abdominal obesity, low HDL-cholesterol, hypertriglyceridemia, high LDL-cholesterol and hypertension (Table 1).

Mean HbA_{1c} reduction from baseline was significantly greater with rimonabant vs. placebo (−0.8% vs. −0.3%, respectively; *P* = 0.0002; Table 2, Fig. 1A). The effect of rimonabant on HbA_{1c} was more pronounced in a subset of patients with baseline HbA_{1c} ≥8.5% (−1.9% vs. −0.7%, respectively; *P* = 0.0009; Table 2). At study end, more patients receiving rimonabant vs. placebo achieved HbA_{1c} <7.0% (51% vs. 35%, respectively; *P*

= 0.0122; Table 2). Fasting plasma glucose also improved significantly with rimonabant compared to placebo (Table 2).

Body weight loss from baseline was greater with rimonabant (−6.7 kg) than placebo (−2.8 kg) at 6 months (Δ −3.84 kg; *P* < 0.0001; Table 2, Fig. 1B), with parallel improvements in waist circumference (−6 vs. −2 cm; *P* < 0.0001; Fig. 1C). In patients with BMI >27 kg/m² at baseline, treatment effects on HbA_{1c}, weight and waist circumference were similar to those observed in the overall population (−0.9% vs. −0.4%, *P* = 0.0009; −7.0 vs. −2.9 kg, *P* < 0.0001; and −6.4 vs. −2.4 cm, *P* < 0.0001, for the rimonabant and placebo groups, respectively).

HDL-cholesterol increased with a treatment difference of +7% (*P* < 0.0001) and triglycerides improved by −17% (*P* = 0.0031) in favor of rimonabant (Table 2, Fig. 1D and 1E). Rimonabant was also associated with significant reductions in non-HDL-cholesterol (Table 2), total cholesterol/HDL-cholesterol ratio, and ApoB/A1 ratio (online Appendix Table A). Total cholesterol and LDL-cholesterol did not change, although the mean size of LDL particles increased significantly with rimonabant relative to placebo (Table 2). Significant improvements occurred with rimonabant versus placebo in levels of adiponectin (Table 2, Fig. 1F), HOMA-IR, proinsulin/insulin ratio (Table 2), proinsulin and leptin levels (online Appendix Table A). Alanine aminotransferase (ALT) levels were reduced by −6.3 UI/L (*P* = 0.0074) in favor of rimonabant 20 mg. Systolic and diastolic blood pressures, heart rate, renal function and urinary albumin/creatinine ratio were not affected by rimonabant.

To explore weight loss and treatment by weight loss interaction, a prespecified linear regression analysis within the ANCOVA model used for the primary analysis suggested that 57% of the placebo-corrected improvement in HbA_{1c} in the overall rimonabant group was not attributable

to body weight changes during treatment. Including weight loss from the ANCOVA model resulted in an adjusted effect on HbA_{1c} of -0.29% for rimonabant vs. placebo ($P = 0.0418$); excluding weight loss also resulted in a significant unadjusted effect on HbA_{1c} for rimonabant vs. placebo (-0.51%; $P = 0.0002$). In the 29 non-overweight patients (BMI ≤ 27 kg/m²), the HbA_{1c} treatment effect of rimonabant was -0.78% vs. placebo, despite weight loss of only -0.53 kg. Furthermore, analysis of HbA_{1c} by three categories of percentage body weight loss also suggested a weight independent effect (online Appendix Table B). Linear regression analysis also indicated that effects of rimonabant on FPG, HDL, triglycerides and adiponectin were not accounted for by weight loss alone.

Safety and tolerability data (Table 3) showed the most common AEs in rimonabant-treated patients were dizziness, nausea, upper respiratory tract infection, anxiety and depressed mood; these were mostly mild or moderate in severity. Overall, 24/138 (17.4%) patients receiving rimonabant experienced a psychiatric disorder vs. 15/140 (10.7%) patients receiving placebo. Within the psychiatric system, anxiety and depressed mood were reported more frequently with rimonabant than placebo, although depression occurred more frequently with placebo vs. rimonabant (2.9% vs. 1.4%, respectively). One patient in the rimonabant group (0.7%) reported suicide ideation, judged by the investigator to be a symptom of depressed mood; no cases of attempted or completed suicide were reported. Hypoglycemia was uncommon: one patient in each group reported a single, mild hypoglycemic event. A higher rate of treatment discontinuation due to AEs largely accounted for a higher overall dropout rate in the rimonabant group (Table 3). A total of 20 SAEs were experienced by five patients from the placebo group and nine patients from the rimonabant group, judged

by the investigators as probably not related to study medication.

CONCLUSIONS

In SERENADE, selective CB₁ receptor antagonism with rimonabant significantly improved HbA_{1c} to a clinically meaningful level close to therapeutic targets, with a greater effect in patients with more severe hyperglycemia at baseline. Furthermore, over 50% of patients treated with rimonabant achieved HbA_{1c} of $<7.0\%$.

Notably, the rimonabant-induced weight loss of 6.7 kg from baseline can also be considered clinically meaningful in light of the concomitant HbA_{1c} reduction of 0.8% from baseline. Acute caloric restriction itself independent of weight loss (18, 19), may have contributed, at least initially, to some of the metabolic improvements observed in SERENADE, but rimonabant-induced weight loss probably contributed significantly to the HbA_{1c} reduction (7). However, linear regression analysis suggested that about half of rimonabant's effect on HbA_{1c} was independent of body weight changes, consistent with improved glycemic control observed in those patients not losing weight. Indeed, patients with BMI ≤ 27 kg/m² had minimal weight loss with rimonabant and still had HbA_{1c} reduction of -0.8%. Controlled pair-feeding studies or studies in normal weight patients may confirm the weight-independent effects of rimonabant.

Preclinical studies with rimonabant demonstrated multiple peripheral metabolic effects, including reduced lipogenesis and free fatty acid synthesis preventing hepatic fat accumulation, increased adiponectin release, and improved skeletal muscle glucose uptake (12, 20–24). These would favorably impact on the T2DM-related metabolic abnormalities. Significant reductions in ALT levels, a marker of fatty liver disease, and increased adiponectin levels observed in

SERENADE suggest a potentially beneficial effect of rimonabant on insulin resistance.

SERENADE confirmed and extended the findings of the RIO-Diabetes study of rimonabant in overweight/obese patients with sub-optimally controlled T2DM on metformin or sulfonylurea monotherapy (15). RIO-Diabetes demonstrated significant reductions in body weight (primary outcome) and a meaningful placebo-subtracted HbA_{1c} reduction (secondary outcome) of 0.7% from a baseline of 7.3%. Improvements in cardiometabolic risk factors in SERENADE were similar to the 1-year interim results of the “Look AHEAD” study, designed to determine the impact of intentional weight loss in reducing cardiovascular events in T2DM (25). However, “Look AHEAD” utilized an intensive lifestyle program with weekly group meetings and monthly individual sessions comprising dietary modifications (meal replacements, frozen foods, structured diets) and increased physical exercise (up to 175 min/week) directed by a multidisciplinary team of dieticians, behavioral psychologists and exercise specialists. Investigators could also initiate weight loss medication and adjustments in blood pressure, lipid and glucose-lowering medications at their discretion. Therefore, direct comparisons between Look AHEAD and SERENADE are difficult.

The safety profile of rimonabant 20 mg in SERENADE was similar to RIO-Diabetes, with most common AEs arising in the psychiatric, neurologic and gastrointestinal systems. Most AEs were mild or moderate in severity in both SERENADE and RIO-Diabetes (15). The incidence of psychiatric disorders was higher with rimonabant versus placebo, and more patients receiving rimonabant experienced anxiety or depressed mood versus placebo. T2DM itself, like many chronic diseases, is associated with an increased incidence of depression. It is currently recommended that rimonabant

should not be used in patients with a history of depression and these potential side effects need to be closely monitored in clinical practice. Further comprehensive safety assessments, using validated neuropsychiatric tools (eg, the Columbia Classification Algorithm for Suicide Assessment), in completed and ongoing studies with rimonabant, will better establish its benefit:risk profile.

In summary, this study demonstrated that rimonabant 20 mg improved glycemic control and reduced body weight, with beneficial effects on the lipid profile, in drug-naïve patients, consistent with previous observations in patients receiving metformin or sulfonylurea. Ongoing clinical trials of rimonabant plus metformin compared with other treatment options will evaluate the potential role of rimonabant, an agent with a novel mechanism of action, in patients with type 2 diabetes (26). Further characterization of the safety profile of rimonabant to better understand the benefit:risk profile will emerge from long-term cardiovascular outcome trials, as well as controlled studies exploring different potential drug combinations between rimonabant and other antidiabetic therapies.

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Table 1–Demographic and disease characteristics at baseline

	Placebo (n = 140)	Rimonabant 20 mg (n = 138)
Mean age (years)	55.5 (10.4)	57.8 (10.5)
Gender (% male)	46.4	52.9
Race (%)		
White	84.3	84.1
Black	3.6	2.2
Asian/Oriental	0.7	1.4
Other	11.4	12.3
Body weight (kg)	96.3 (21.0)	96.6 (21.1)
BMI (kg/m ²)	34.6 (6.9)	34.4 (6.6)
BMI >27 kg/m ² (%)	89.3	89.9
BMI ≥30 kg/m ² (%)	72.9	72.5
Mean waist circumference (cm)	108.8 (14.8)	108.7 (13.6)
High waist circumference (% men/% women)*	70.8/88.0	66.7/90.8
Diabetes duration (months)	15.1 (13.4)	16.0 (11.2)
Family history of T2DM (%)	52.1	46.4
HbA _{1c} (%)	7.9 (0.7)	7.9 (0.8)
HbA _{1c} ≥8.5% and ≤10% (%)	25.7	25.4
FPG (mmol/L)	8.7 (1.9)	9.0 (1.9)
Concomitant anti-dyslipidemia medication (%)	35.7	29.7
Concomitant anti-hypertensive medication (%)	67.1	62.3

Unless otherwise noted, values are Means (SD). *Waist circumference >102 cm (men) or >88 cm (women).

Table 2—Clinical efficacy of rimonabant

	Placebo	Rimonabant 20 mg	P value vs placebo
HbA_{1c} (% units)			
All patients			
<i>n</i>	131	130	
Mean baseline (SD)	7.9 (0.7)	7.9 (0.8)	
Mean change vs. baseline (SD)	-0.3 (1.2)	-0.8 (1.2)	
LS Mean change vs. placebo (SE)	-	-0.51 (0.14)	0.0002
HbA _{1c} <6.5% at 6 months (%) (<i>n</i>)	16.0 (21)	23.8 (31)	0.0930
HbA _{1c} <7.0% at 6 months (%) (<i>n</i>)	35.1 (46)	50.8 (66)	0.0122
Patients with HbA_{1c} ≥8.5%			
<i>n</i>	31	34	
Mean baseline (SD)	8.9 (0.3)	8.9 (0.5)	
Mean change vs. baseline (SD)	-0.7 (1.7)	-1.9 (1.1)	
LS Mean change vs. placebo (SE)	-	-1.25 (0.36)	0.0009
Fasting plasma glucose (mmol/L)			
<i>n</i>	126	123	
Mean baseline (SD)	8.6 (1.7)	9.1 (2.0)	
Mean change vs. baseline (SD)	0.1 (2.1)	-0.9 (2.3)	
LS Mean change vs. placebo (SE)	-	-0.83 (0.25)	0.0012
Body weight (kg)			
<i>n</i>	138	135	
Mean baseline (SD)	96.0 (20.9)	96.6 (21.1)	
Mean change vs. baseline (SD)	-2.8 (4.8)	-6.7 (5.5)	
LS Mean change vs. placebo (SE)	-	-3.84 (0.61)	<0.0001
Waist circumference (cm)			
<i>n</i>	131	129	
Mean baseline (SD)	108 (15)	109 (14)	
Mean change vs. baseline (SD)	-2 (5)	-6 (6)	
LS Mean change vs. placebo (SE)	-	-3.7 (0.7)	<0.0001
Adiponectin (µg/mL)			
<i>n</i>	128	127	
Mean baseline (SD)	6.0 (3.9)	5.5 (3.3)	
Mean change vs. baseline (SD)	-0.2 (2.9)	1.6 (4.0)	
LS Mean change vs. placebo (SE)	-	1.60 (0.41)	0.0001
HOMA-IR			
<i>n</i>	126	119	
Mean baseline (SD)	7.1 (5.8)	7.8 (8.9)	
Mean change vs. baseline (SD)	0.3 (7.6)	-1.9 (7.7)	
LS Mean change vs. placebo (SE)	-	-1.9 (0.7)	0.0098
Proinsulin/Insulin			
<i>n</i>	128	126	
Mean baseline (SD)	0.59 (0.36)	0.63 (0.49)	
Mean change vs. baseline (SD)	-0.04 (0.39)	-0.17 (0.43)	
LS Mean change vs. placebo (SE)	-	-0.10 (0.04)	0.0135
HDL-cholesterol			
<i>n</i>	131	130	
Mean baseline (mmol/L) (SD)	1.29 (0.28)	1.31 (0.33)	
Mean % change vs. baseline (SD)	3.15 (12.16)	10.05 (17.04)	
LS Mean % change vs. placebo (SE)	-	7.30 (1.75)	<0.0001
Triglycerides			
<i>n</i>	131	129	
Mean baseline (mmol/L) (SD)	2.09 (1.02)	2.35 (1.64)	
Mean % change vs. baseline (SD)	4.35 (58.12)	-16.33 (32.76)	
LS Mean change vs. placebo (SE)	-	-17.28 (5.78)	0.0031

LDL-cholesterol			
<i>n</i>	131	130	
Mean baseline (mmol/L) (SD)	3.31 (0.85)	3.41 (0.93)	
Mean % change vs. baseline (SD)	1.35 (28.14)	-1.80 (26.04)	
LS Mean % change vs. placebo (SE)	-	-1.475 (3.147)	0.6396
LDL particle size			
<i>n</i>	129	126	
Mean baseline (Å) (SD)	268.6 (4.7)	268.3 (5.6)	
Mean % change vs. baseline (SD)	-0.0 (1.6)	0.6 (1.7)	
LS Mean % change vs. placebo (SE)	-	0.61 (0.18)	0.0008
Non-HDL-cholesterol			
<i>n</i>	131	130	
Mean baseline (mmol/L) (SD)	3.78 (0.95)	3.99 (1.14)	
Mean % change vs. baseline (SD)	2.72 (26.42)	-4.64 (19.55)	
LS Mean % change vs. placebo (SE)	-	-5.535 (2.763)	0.0462
Total cholesterol			
<i>n</i>	131	130	
Mean baseline (mmol/L) (SD)	5.07 (0.96)	5.31 (1.14)	
Mean % change vs. baseline (SD)	2.01 (17.25)	-1.43 (15.09)	
LS Mean % change vs. placebo (SE)	-	-1.961 (1.903)	0.3037

Mean changes versus placebo are least squares (LS) mean changes from the ANCOVA analysis (see Methods). Data are from the ITT population (last observation carried forward) excluding post rescue medication data.

SD, standard deviation; SE, standard error

Table 3–Summary of adverse events at 6 months in randomized and exposed patients**Treatment-emergent adverse events occurring with an incidence of $\geq 2\%$ in the rimonabant treatment group listed by preferred term***

	Placebo n = 140 (%)	Rimonabant 20 mg n = 138 (%)
Any adverse event	81 (57.9)	97 (70.3)
Dizziness	3 (2.1)	15 (10.9)
Nausea	5 (3.6)	12 (8.7)
Nasopharyngitis	11 (7.9)	10 (7.2)
Upper respiratory tract infection	3 (2.1)	10 (7.2)
Anxiety	5 (3.6)	8 (5.8)
Depressed mood	1 (0.7)	8 (5.8)
Diarrhea	6 (4.3)	6 (4.3)
Vertigo	1 (0.7)	6 (4.3)
Vomiting	1 (0.7)	6 (4.3)
Asthenia	1 (0.7)	5 (3.6)
Headache	9 (6.4)	5 (3.6)
Anorexia	0	4 (2.9)
Back pain	4 (2.9)	4 (2.9)
Fall	3 (2.1)	4 (2.9)
Fatigue	1 (0.7)	4 (2.9)
Paresthesia	2 (1.4)	4 (2.9)
Sinusitis	2 (1.4)	4 (2.9)
Vision blurred	0	4 (2.9)
Arthralgia	4 (2.9)	3 (2.2)
Dry mouth	0	3 (2.2)
Hypoesthesia	0	3 (2.2)
Influenza	2 (1.4)	3 (2.2)
Insomnia	3 (2.1)	3 (2.2)
Pain	1 (0.7)	3 (2.2)
Shoulder pain	1 (0.7)	3 (2.2)
Somnolence	0	3 (2.2)
Visual acuity reduced	0	3 (2.2)
Adverse events leading to permanent study discontinuation		
Overall dropout rate	15 (10.7)	27 (19.6)
Any serious adverse event**	5 (3.6)	9 (6.5)
Discontinuation due to any adverse event†	3 (2.1)	13 (9.4)
Psychiatric disorders		
Any psychiatric adverse event	0	7 (5.1)
Depressed mood	0	3 (2.2)
Nervous system disorders		
Any nervous system adverse event	0	5 (3.6)
Paresthesia	0	3 (2.2)
Dizziness	0	2 (1.4)
Hyposmia	0	2 (1.4)
Gastrointestinal disorders		
Any gastrointestinal system adverse event	1 (0.7)	4 (2.9)
Metabolism and nutrition disorders		

Any adverse event related to metabolism or nutrition	0	2 (1.4)
Anorexia	0	2 (1.4)

Data are number (%). One patient can report several events.

* Defined according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

**One patient died (during treatment with placebo) as a result of a subdural hemorrhage secondary to a meningioma.

† According to MedDRA, at least two patients in any rimonabant group and only in main system organ classes (1%).

FIGURE LEGEND

Figure 1—Mean (SE) changes from baseline in HbA_{1c} (A), body weight (B), waist circumference (C), HDL-cholesterol (D), triglycerides (E) and adiponectin (F) over 6 months in the intention-to-treat population with last observation carried forward.



