SERENADE: The Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients

Effects of monotherapy with rimonabant, the first selective CB_1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes

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OBJECTIVE — The purpose of this study was to assess the glucose-lowering efficacy and safety of rimonabant monotherapy in drug-naive type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — The Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients (SERENADE) was a 6-month, randomized, double-blind, placebo-controlled trial of 20 mg/day rimonabant in drug-naive patients with type 2 diabetes (A1C 7–10%). The primary end point was A1C change from baseline; secondary end points included body weight, waist circumference, and lipid profile changes.

RESULTS — A total of 281 patients were randomly assigned; 278 were exposed to treatment, and 236 (84.9%) completed the study. Baseline A1C (7.9%) was reduced by −0.8% with rimonabant versus −0.3% with placebo (Δ A1C −0.51%; $P = 0.0002$), with a larger rimonabant effect in patients with baseline A1C ≥8.5% (Δ A1C −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 were 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-naive type 2 diabetic patients. Further ongoing studies will better establish the benefit-to-risk profile of rimonabant and define its place in type 2 diabetes management.

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An increasing worldwide burden of type 2 diabetes 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 type 2 diabetes, which contribute substantially to the increased cardiovascular risk in this population (3–5).

Comprehensive type 2 diabetes 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 type 2 diabetic patients; 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 (CB_1) receptors located in the brain, adipose tissue, liver, skeletal muscle, and pancreas (12,13). CB_1 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 type 2 diabetes (14).

Rimonabant, a selective CB_1 receptor antagonist, has been shown to reduce body weight and improve glycemic control in overweight/obese patients with type 2 diabetes suboptimally controlled with metformin or sulfonylurea monotherapy (15). We report the results of the Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients (SERENADE), an exploratory study to assess the glucose-lowering efficacy and safety of rimonabant monotherapy in drug-naive type 2 diabetes and the first trial to use A1C as the primary end point.

RESEARCH DESIGN AND METHODS

Patients

This randomized, double-blind, parallel-group, placebo-controlled, multinational study recruited patients from 56 centers (22 March 2005–10 June 2006). Eligible type 2 diabetic (16) patients were aged ≥18 years with duration of diabetes

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of >2 months but <3 years and with A1C ≥7 and ≤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 the previous 3 months, pregnancy or lactation, use of antiobesity treatments within the previous 3 months, changes to lipid-modifying treatments within the previous 2 months, and any clinically significant disorders (endocrine/metabolic/severe psychological disorders, presence/history of cancer, or 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

After a 1- to 2-week screening period with instructions not to change diet, patients were randomly assigned to double-blind rimonabant (20 mg) or matching placebo (1:1 ratio) for 6 months. Randomization was stratified according to A1C at screening (≥7 to <8.5% or ≥8.5 to ≤10%). All patients received American Diabetes Association dietary recommendations (6) from a dietitian at baseline and reinforcement at the 3- and 6-month study visits. Overweight (BMI ≥27 to <30 kg/m^2) or obese (BMI ≥30 kg/m^2) patients were instructed to follow a 600-kcal/day caloric deficit. All patients were encouraged to increase physical activity.

The primary study end point was absolute change in A1C from baseline to study end (month 6). Prespecified secondary efficacy parameters, as in any antidiabetes trial, included the proportion of patients achieving predefined glycemic targets (A1C <6.5 or <7%) and changes in fasting plasma glucose (FPG), body weight, waist circumference, HDL cholesterol, triglycerides, LDL particle size, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β-cell function, adiponectin, leptin, ghrelin, blood pressure, and urinary albumin-to-creatinine ratio (17). Patients with A1C >9% at 3 months confirmed by a repeat measurement 1 month later could receive rescue medication at the investigator's discretion.

Table 1—*Demographic and disease characteristics at baseline*

	Placebo	20 mg rimonabant
n	140	138
Age (years)	55.5 ± 10.4	57.8 ± 10.5
Male sex	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
>27	89.3	89.9
≥30	72.9	72.5
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 type 2 diabetes	52.1	46.4
A1C (%)	7.9 ± 0.7	7.9 ± 0.8
A1C ≥8.5 and ≤10	25.7	25.4
FPG (mmol/l)	8.7 ± 1.9	9.0 ± 1.9
Concomitant antidyslipidemia medication	35.7	29.7
Concomitant antihypertensive medication	67.1	62.3

Data are means ± SD or %. *Waist circumference >102 cm (men) or >88 cm (women).

Measurements

Primary and secondary efficacy parameters were measured at screening and/or baseline and at 3 and 6 months after random assignment. Body weight and vital signs were measured at screening, at baseline, and monthly thereafter.

Blood samples for measurement of metabolic parameters were taken under fasting conditions and were analyzed at a central laboratory (MDS Diagnostic Services, Mississauga, ON, Canada). A1C was measured using ion-exchange high-pressure liquid chromatography with Diabetes Control and Complications Trial reference values.

Safety analyses were based on standard adverse event reporting. All adverse events were coded using the global Medical Dictionary for Regulatory Activities (MedDRA) (version 9.0). Adverse events were analyzed using MedDRA by system organ classification and the subcategory, preferred term (which represents a single medical concept). 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://dx.doi.org/10.2337/dc08-0386). Any adverse event related to a depressive disorder or neurological adverse event was captured by patients self-reporting the event to the investigator and recorded in a standard adverse event/serious adverse event form for each episode; a questionnaire was then completed and the adverse event or /serious adverse event was coded using MedDRA terminology. Symptoms were only recorded when the diagnosis was unknown. Any adverse event or serious adverse event 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 A1C of −0.8% between the 20 mg rimonabant and placebo groups at 6 months (SD for the change in A1C from baseline 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. The ITT popula-

Table 2—*Clinical efficacy of rimonabant*

	Placebo	20 mg rimonabant	*P* value vs. placebo
A1C			
All patients			
n	131	130	
Mean baseline (%)*	7.9 ± 0.7	7.9 ± 0.8	
Mean change vs. baseline (%)*	–0.3 ± 1.2	–0.8 ± 1.2	
LS mean change vs. placebo (%)†	—	–0.51 ± 0.14	0.0002
A1C <6.5% at 6 months	16.0 (21)	23.8 (31)	0.0930
A1C <7.0% at 6 months	35.1 (46)	50.8 (66)	0.0122
Patients with A1C ≥8.5%			
n	31	34	
Mean baseline (%)*	8.9 ± 0.3	8.9 ± 0.5	
Mean change vs. baseline (%)*	–0.7 ± 1.7	–1.9 ± 1.1	
LS mean change vs. placebo (%)†	—	–1.25 ± 0.36	0.0009
Fasting plasma glucose (mmol/l)			
n	126	123	
Mean baseline*	8.6 ± 1.7	9.1 ± 2.0	
Mean change vs. baseline*	0.1 ± 2.1	–0.9 ± 2.3	
LS mean change vs. placebo†	—	–0.83 ± 0.25	0.0012
Body weight (kg)			
n	138	135	
Mean baseline*	96.0 ± 20.9	96.6 ± 21.1	
Mean change vs. baseline*	–2.8 ± 4.8	–6.7 ± 5.5	
LS mean change vs. placebo†	—	–3.84 ± 0.61	<0.0001
Waist circumference (cm)			
n	131	129	
Mean baseline*	108 ± 15	109 ± 14	
Mean change vs. baseline*	–2 ± 5	–6 ± 6	
LS mean change vs. placebo†	—	–3.7 ± 0.7	<0.0001
Adiponectin (μg/ml)			
n	128	127	
Mean baseline*	6.0 ± 3.9	5.5 ± 3.3	
Mean change vs. baseline*	–0.2 ± 2.9	1.6 ± 4.0	
LS mean change vs. placebo†	—	1.60 ± 0.41	0.0001
HOMA-IR			
n	126	119	
Mean baseline*	7.1 ± 5.8	7.8 ± 8.9	
Mean change vs. baseline*	0.3 ± 7.6	–1.9 ± 7.7	
LS mean change vs. placebo†	—	–1.9 ± 0.7	0.0098
Proinsulin/insulin			
n	128	126	
Mean baseline*	0.59 ± 0.36	0.63 ± 0.49	
Mean change vs. baseline*	–0.04 ± 0.39	–0.17 ± 0.43	
LS mean change vs. placebo†	—	–0.10 ± 0.04	0.0135
HDL cholesterol (mmol/l)			
n	131	130	
Mean baseline*	1.29 ± 0.28	1.31 ± 0.33	
Mean % change vs. baseline*	3.15 ± 12.16	10.05 ± 17.04	
LS mean % change vs. placebo†	—	7.30 ± 1.75	<0.0001
Triglycerides (mmol/l)			
n	131	129	
Mean baseline*	2.09 ± 1.02	2.35 ± 1.64	
Mean % change vs. baseline*	4.35 ± 58.12	–16.33 ± 32.76	
LS mean % change vs. placebo†	—	–17.28 ± 5.78	0.0031
LDL cholesterol (mmol/l)			
n	131	130	
Mean baseline*	3.31 ± 0.85	3.41 ± 0.93	
Mean % change vs. baseline*	1.35 ± 28.14	–1.80 ± 26.04	
LS mean % change vs. placebo†	—	–1.475 ± 3.147	0.6396

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Table 2—*Continued*

	Placebo	20 mg rimonabant	*P* value vs. placebo
LDL particle size (Å)			
n	129	126	
Mean baseline*	268.6 ± 4.7	268.3 ± 5.6	
Mean % change vs. baseline*	–0.0 ± 1.6	0.6 ± 1.7	
LS Mean % change vs. placebo†	—	0.61 ± 0.18	0.0008
Non-HDL cholesterol (mmol/l)			
n	131	130	
Mean baseline*	3.78 ± 0.95	3.99 ± 1.14	
Mean % change vs. baseline*	2.72 ± 26.42	–4.64 ± 19.55	
LS mean % change vs. placebo†	—	–5.535 ± 2.763	0.0462
Total cholesterol (mmol/l)			
n	131	130	
Mean baseline*	5.07 ± 0.96	5.31 ± 1.14	
Mean % change vs. baseline*	2.01 ± 17.25	–1.43 ± 15.09	
LS mean % change vs. placebo†	—	–1.961 ± 1.903	0.3037

Data are means ± *SD or †SE or percent (*n*). Mean changes versus placebo are least-squares (LS) mean changes from the ANCOVA analysis (see RESEARCH DESIGN AND METHODS). Data are from the ITT population (last observation carried forward) excluding postrescue medication data.

tion comprised all patients who received at least one dose of double-blind treatment and had at least one assessment after random assignment. All efficacy data obtained after the introduction of rescue medication were excluded from the analysis. The safety population included all patients randomly assigned and exposed to treatment. For descriptive data for adverse events, statistical analyses were not performed; descriptive data were reported using numbers and percentages of patients.

Statistical analyses were performed using SAS (version 8.2, SAS Institute, Cary, NC). Continuous variables were measured using repeated-measures ANCOVA, with treatment, country, and randomization stratum as fixed effects and baseline assessment as the covariate. Categorical data were analyzed using a Cochran-Mantel-Haenszel test stratified on country and randomization stratum. *P* values were two sided and unadjusted.

RESULTS — In total, 281 patients were randomly assigned to 20 mg rimonabant ($n = 140$) or placebo ($n = 141$) (supplemental Fig. 1, available in the online appendix). 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 randomly assigned 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 (adverse events 13, patient request 8, lost to follow-up 2, poor compliance 1, and other reasons 3) versus 15 patients receiving placebo (lack of efficacy 4, lost to follow-up 4, adverse events 3, patient request 3, and other reasons 1). Rescue medication was required for 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 A1C was 7.9%, and most participants were overweight or obese (90% had BMI >27 kg/m^2). There was a high prevalence of cardiometabolic risk factors, including abdominal obesity, low HDL cholesterol, hypertriglyceridemia, high LDL cholesterol, and hypertension (Table 1).

Mean A1C reduction from baseline was significantly greater with rimonabant versus placebo (−0.8 vs. −0.3%, respectively; $P = 0.0002$) (Table 2, Fig. 1*A*). The effect of rimonabant on A1C was more pronounced in a subset of patients with baseline A1C ≥8.5% (−1.9 vs. −0.7%, respectively; $P = 0.0009$) (Table 2). At study end, more patients receiving rimonabant than patients receiving placebo achieved A1C <7.0% (51 vs. 35%, respectively; $P = 0.0122$) (Table 2). FPG also improved significantly with rimonabant compared with placebo (Table 2).

Body weight loss from baseline was greater with rimonabant (−6.7 kg) than with placebo (−2.8 kg) at 6 months (Δ −3.84 kg; $P < 0.0001$) (Table 2, Fig. 1*B*), with parallel improvements in waist circumference (−6 vs. −2 cm; $P < 0.0001$) (Fig. 1*C*). In patients with BMI >27 kg/m^2 at baseline, treatment effects on A1C, 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. 1*D* and *E*). Rimonabant was also associated with significant reductions in non-HDL cholesterol (Table 2), total cholesterol–to–HDL cholesterol ratio, and apolipoprotein B–to–apolipoprotein A1 ratio (supplemental Table A, available in the online appendix). 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. 1*F*), HOMA-IR, proinsulin-to-insulin ratio (Table 2), and proinsulin and leptin levels (supplemental Table A). Alanine aminotransferase levels were reduced by −6.3 IU/l ($P = 0.0074$) in favor of 20 mg rimonabant. Systolic and diastolic blood pressures, heart rate, renal function, and urinary albumin-to-creatinine ratio were not affected by rimonabant.

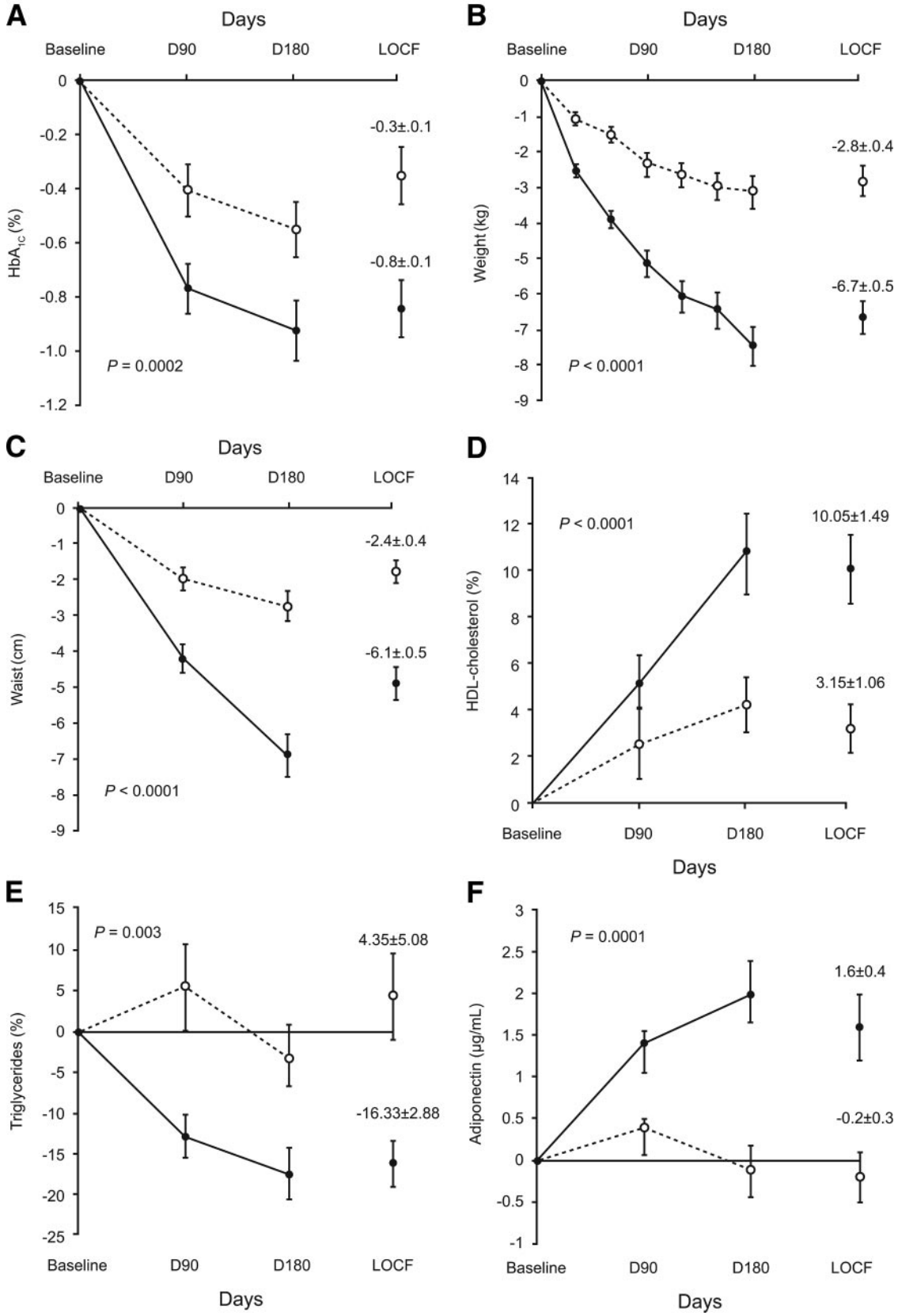

Figure 1—*Mean (SE) changes from baseline in A1C* (A)*, body weight* (B)*, waist circumference* (C)*, HDL cholesterol* (D)*, triglycerides* (E)*, and adiponectin* (F) *over 6 months in the intention-to-treat population with last observation carried forward.* ○ *with dotted line, placebo;* ● *with regular line, rimonabant.*

Table 3—*Summary of adverse events at 6 months in randomly assigned and exposed patients*

Treatment-emergent adverse events occurring with an incidence of ≥2% in the rimonabant treatment group listed by preferred term*	Placebo	20 mg rimonabant
n	140	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 *n* (%). One patient can report several events. *Defined according to the MedDRA classification. †One patient died (during treatment with placebo) as a result of a subdural hemorrhage due to a meningioma. ‡According to MedDRA, at least two patients in any rimonabant group and only in main system organ classes (1%).

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 A1C in the overall rimonabant group was not attributable to body weight changes during treatment. Including weight loss in the ANCOVA model resulted in an adjusted effect on A1C of −0.29% for rimonabant versus placebo ($P = 0.0418$); excluding weight loss also resulted in a significant unadjusted effect on A1C for rimonabant versus placebo (−0.51%; $P = 0.0002$). In the 29 patients who were not overweight (BMI ≤27 kg/m^2), the A1C treatment effect of rimonabant was −0.78% versus placebo, despite weight loss of only −0.53 kg. Furthermore, analysis of A1C by three categories of percent body weight loss also suggested a weight-independent effect (supplemental Table B, available in the online appendix). Linear regression analysis also indicated that the effects of rimonabant on FPG, HDL, triglycerides, and adiponectin were not accounted for by weight loss alone.

Safety and tolerability data (Table 3) showed that the most common adverse events 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 of 138 (17.4%) patients receiving rimonabant experienced a psychiatric disorder versus 15 of 140 (10.7%) patients receiving placebo. Within the psychiatric system, anxiety and depressed mood were reported more frequently with rimonabant than with placebo, although depression occurred more frequently with placebo than with 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 adverse events largely accounted for a higher overall dropout rate in the rimonabant group (Table 3). A total of 20 severe adverse events were experienced by five patients from the placebo group and nine patients from the rimonabant group and were judged by the investigators as probably not being related to the study medication.

CONCLUSIONS — In SERENADE, selective CB_1 receptor antagonism with rimonabant significantly improved A1C to a clinically meaningful level close to therapeutic targets, with a greater effect in patients with more severe hyperglycemia at baseline. Furthermore, >50% of patients treated with rimonabant achieved A1C 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 A1C 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 A1C reduction (7). However, linear regression analysis suggested that about half of the effect of rimonabant on A1C was independent of body weight changes, consistent with improved glycemic control observed in those patients not losing weight. Indeed, patients with BMI ≤27 kg/m^2 had minimal weight loss with rimonabant and still had an A1C 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 type 2 diabetes–related metabolic abnormalities. Significant reductions in levels of alanine aminotransferase, a marker of fatty liver disease, and increased adiponectin levels observed in SERENADE suggested a potentially beneficial effect of rimonabant on insulin resistance.

SERENADE confirmed and extended the findings of the Rimonabant in Obesity (RIO)-Diabetes study of rimonabant in overweight/obese patients with type 2 diabetes suboptimally controlled using metformin or sulfonylurea monotherapy (15). The RIO-Diabetes study demonstrated significant reductions in body weight (primary outcome) and a meaningful placebo-subtracted A1C 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 (Action for Health in Diabetes) study designed to determine the impact of intentional weight loss in reducing cardiovascular events in type 2 diabetes (25). However, the Look AHEAD study used an intensive lifestyle program with weekly group meetings and monthly individual sessions comprising dietary modifications (meal replacements, frozen foods, and structured diets) and increased physical exercise (up to 175 min/week) directed by a multidisciplinary team of dietitians, 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 results from the Look AHEAD study and SERENADE are difficult.

The safety profile of 20 mg rimonabant in SERENADE was similar to that in RIO-Diabetes, with the most common adverse events arising in the psychiatric, neurological, and gastrointestinal systems. Most adverse events 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. Type 2 diabetes 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 (e.g., the Columbia Classification Algorithm for Suicide Assessment) in completed and ongoing studies with rimonabant will better establish its benefit-to-risk profile.

In summary, this study demonstrated that 20 mg rimonabant improved glycemic control and reduced body weight, with beneficial effects on the lipid profile, in drug-naive 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-to-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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