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Efficacy and Safety of Rimonabant for Improvement of Multiple Cardiometabolic Risk Factors in Overweight/Obese Patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program*

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ABSTRACT

Objective — To better define the efficacy and safety of rimonabant, the first selective cannabinoid type 1 (CB_1) receptor antagonist, in a large population of overweight and obese patients using pooled efficacy data from three Phase III nondiabetes Rimonabant in Obesity and Related Metabolic Disorders (RIO) studies, selected efficacy data from the RIO-Diabetes study, and pooled safety data for all four RIO studies.

Research design and methods — The RIO studies enrolled patients who were either overweight (BMI >27 kg/m^2) with at least one comorbidity (i.e., hypertension, dyslipidemia, or, for RIO-Diabetes, type 2 diabetes) or obese. All patients received daily treatment with rimonabant (5 or 20 mg) or placebo for 1 year plus a hypocaloric diet (600 kcal/day deficit) and advice on increased physical activity. RIO-Europe (n = 1,508), RIO-North America (n = 3,045), and RIO-Lipids (n = 1,036) excluded patients with type 2 diabetes; untreated dyslipidemia was an entry requirement for RIO-Lipids. RIO-Diabetes (n = 1,047) required the presence of type 2 diabetes inadequately controlled by sulfonylurea or metformin monotherapy.

Results — The pooled intention-to-treat population comprised 5,580 patients without diabetes (3,165 completed treatment) and 1,047 patients with diabetes (692 completed treatment). Most efficacy measures improved during the 4-week placebo run-in period, except that HDL cholesterol decreased as expected in the early phase of a hypocaloric diet. After 1 year of randomized treatment, changes from baseline with 20 mg rimonabant in the nondiabetic population were as follows: body weight -6.5 kg, waist circumference -6.4 cm, HDL cholesterol +16.4%, triglycérides -6.9%, fasting insulin -0.6 µU/ml, and homeostasis model assessment for insulin resistance (HOMA-IR) -0.2 (all $P < 0.001$ vs. placebo). In the diabetic population, 20 mg rimonabant reduced A1C levels by 0.6% ($P < 0.001$ vs. placebo). Regression analysis of change in HDL cholesterol, triglycérides, adiponectin (in RIO-Lipids), and A1C (in RIO-Diabetes) versus body weight at 1 year by ANCOVA suggested that 45-57% of the effect of rimonabant could not be explained by the observed weight loss. At 1 year, adverse events more frequently reported with rimonabant were gastrointestinal, neurological, and psychiatric in nature. Serious adverse events were infrequent and almost equivalent to placebo. Overall discontinuation rates were similar across treatment groups, except discontinuation from adverse events, which occurred more frequently with 20 mg rimonabant versus placebo (most commonly, depressive disorders [1.9 vs. 0.8%], nausea [1.4 vs. 0.1%], mood alterations with depressive symptoms [1.0 vs. 0.6%], and anxiety [1.0 vs. 0.3%]). A thorough review of psychiatric and neurological adverse events was performed.

Conclusions — In overweight/obese patients, 20 mg/day rimonabant produced weight loss and significant improvements in multiple cardiometabolic risk factors such as waist circumference, A1C, HDL cholesterol, and triglycérides. Rimonabant was generally well tolerated, with more frequently reported adverse events being

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gastrointestinal, neurological, and psychiatric in nature.

Abbreviations: BP, blood pressure; HOMA-IR, homeostasis model assessment for insulin resistance; ITT, intention-to-treat; RIO, Rimonabant in Obesity and Related Metabolic Disorders.

Cardiovascular disease remains the leading cause of death worldwide, despite a growing range of treatment options and preventive measures, such as antihypertensive, antidiabetic, and LDL cholesterol-lowering medicines and smoking cessation campaigns. A constellation of cardiovascular risk factors and markers, such as low HDL cholesterol, hypertriglyceridemia, and elevated blood glucose and insulin levels, are clustered in patients with abdominal obesity. These patients are reaching epidemic proportions worldwide (1-3). Novel treatments that address this cluster by modifying a common underlying mechanism may provide a new therapeutic option for reducing multiple cardiometabolic risk factors.

Recent studies in animal models and humans in the clinical setting (4-7) linked the recently discovered endocannabinoid system and its cannabinoid type 1 (CB_1) receptor to obesity and its associated risk factors and also to type 2 diabetes. These receptors are expressed in adipocytes (8), liver (9), pancreas (10), brain (11), gut (12), and skeletal muscle (13). Endocannabinoid system dysregulation has been demonstrated in the brain (11), adipose tissue (14), liver (9), and pancreas (5) in animal models of obesity. In humans, increased endocannabinoid levels are associated with intra-abdominal obesity (4,5,15,16), type 2 diabetes (5), and binge-eating disorder (6). A genetic polymorphism of one of the enzymes responsible for endocannabinoid breakdown (fatty acid amide hydrolase) has been linked with overweight and obesity (7). CB_1 receptor blockade in isolated adipocytes increases expression of adiponectin, which is reduced in obesity and type 2 diabetes, and promotes weight loss and insulin sensitivity (14). Thus, the endocannabinoid system is regarded as an integrated physiologic system that modulates nutrient intake, transport, metabolism, and storage, for which dysfunction is associated with abdominal adiposity and its associated comorbidities.

The Rimonabant in Obesity and Related Metabolic Disorders (RIO) program comprises four large multicenter randomized Phase III trials of similar design, undertaken in over 5,500 overweight and obese nondiabetic patients with or without comorbidities (RIO-Lipids [17], RIO-Europe [18], and RIO-North America [19)] and in 1,047 patients with type 2 diabetes (RIO-Diabetes [20]). Results from these four trials show that after 1 year of treatment, 20 mg rimonabant given once daily produced significant improvements in weight loss; reductions in waist circumference, A1C, and triglycerides; and increased HDL cholesterol compared with placebo (17-20). The present report combines a pooled analysis of efficacy in the three studies in patients without diabetes (RIO-Lipids, RIO-Europe, and RIO-North America) and selected efficacy data from the previously reported RIO-Diabetes study (20) with a summary of pooled safety data from all four RIO studies. This analysis was conducted to better define the magnitude of the effects of rimonabant on primary and secondary end points in a large population without diabetes and to consolidate safety and tolerability data across all four Phase III trials.

Research design and methods

All four RIO trials were initiated between August and December 2001 and used a similar study design to allow a pooled analysis of the data. Each study was double-blinded and placebo-controlled, with three parallel treatment groups (5 mg or 20 mg rimonabant or placebo, given once daily) and used a 2-week screening period and a 4-week placebo run-in period. The studies were conducted in 14 countries including a number from North America and Europe, plus Argentina and Australia.

The detailed study designs and inclusion/exclusion criteria have been reported previously (17-20). In brief, RIO-Europe and RIO-North America were 2-year studies including overweight adult patients (BMI >27 kg/m^2) with at least one comorbidity (hypertension or dyslipidemia) or obese patients (BMI ≥ 30 kg/m^2) with or without comorbidities and excluding those with a history of major depression, defined as necessitating hospitalization, two or more recurrent episodes of depression, or suicide attempt. Weight-altering medications (antiobesity drugs, corticosteroids, antidepressants, neuroleptics, nonselective systemic antihistamines, and nicotine substitutes) were not permitted. RIO-Lipids was a 1-year study that required the presence of untreated dyslipidemia, defined as triglycerides ≥ 1.69 mmol/l or a ratio of total cholesterol: HDL cholesterol >4.5 in women or >5 in men. RIO-Diabetes was also a 1-year study that required type 2 diabetes inadequately controlled with metformin or sulfonylurea monotherapy for at least 6 months, defined as A1C levels of 6.5-10.0%.

During the 4-week single-blind placebo run-in period, a mild hypocaloric diet (to achieve a 600 kcal/day deficit), along with encouragement to increase physical activity levels, was introduced. Thereafter, eligible patients were stratified by weight loss during the run-in (greater or less than 2 kg) and randomly allocated to daily treatment with either rimonabant (5 or 20 mg) or placebo for 1 year in a ratio (placebo:rimonabant, 5 mg:20 mg

rimonabant) of either 1:2:2 (RIO-Europe and RIO-North America) or 1:1:1 (RIO-Lipids and RIO-Diabetes). Monthly treatment visits included standardized assessments of body weight, waist circumference, blood pressure (BP), smoking status, and concomitant medications, together with reinforcement of diet and exercise recommendations.

Fasting lipid profile, glucose, and insulin were analyzed every 3 months by ICON Laboratories (Farmingdale, NY, and Dublin, Ireland). Insulin resistance using the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin (μU/ml) × fasting glucose (mmol/l)/22 .5 . The prevalence of metabolic syndrome was assessed at baseline and 1 year according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (21).

Populations and end points in studies pooled for analysis

The pooled intention-to-treat (ITT) population consisted of 5,580 RIO-Europe, RIO-North America, and RIO-Lipids patients (nine randomized patients never received the study drug and were excluded from the pooled ITT population), of whom 1,254 received placebo, 4,326 received rimonabant (2,162 on 5 mg and 2,164 on 20 mg), and 3,165 completed the 1-year study. The pooled safety population consisted of 1,602, 2,520, and 2,503 patients (placebo, 5 mg and 20 mg, respectively) in the four RIO studies. This study reports only the 20 mg data (the dose that is approved and available in many countries [22]).

The primary efficacy end point in all RIO studies was the absolute reduction in body weight after 1 year of treatment in the ITT population compared with the baseline (randomization) value. The secondary end points in all four studies were the proportion of patients who achieved weight loss from baseline of either ≥5 or ≥10% at 1 year, and the changes from baseline in waist circumference; levels of HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose, and fasting insulin; total cholesterol-to-HDL cholesterol ratio; insulin resistance; and prevalence of metabolic syndrome. Change from baseline in A1C was a secondary end point in the RIO-Diabetes study. Changes in resting systolic and diastolic BP were also assessed as secondary efficacy end points.

Tolerability was assessed by evaluation of adverse events. Safety assessments consisted of clinical laboratory tests, electrocardiogram, vital signs, and administration of the Hospital Anxiety and Depression Scale questionnaire (23,24). A more extensive additional safety analysis is available at www.fda.gov (25).

Statistical methods

Analyses were performed on the ITT populations (efficacy and safety). The ITT population consisted of all randomized patients who received at least one dose of study drug and had at least one post-baseline assessment. For patients with missing end point values in the ITT population, the last post-baseline value was used to calculate the change from baseline (last observation carried forward). The safety population consisted of all randomized patients who received at least one dose of study drug.

Change from baseline at 1 year was analyzed using an ANOVA model with treatment and study as fixed effects. The ANOVA model for weight also included a term for randomization stratum (weight loss ≤2 kg or >2 kg during placebo run-in).

All continuous end points were assessed as absolute changes from baseline to 1 year, except for HDL cholesterol, LDL cholesterol, and triglycerides, which were assessed as percentage changes from baseline. The percentage of patients who achieved at least a 5 or 10% body weight loss at 1 year was analyzed using a logistic regression model. The prevalence of metabolic syndrome was analyzed using logistic regression, with treatment and study as fixed effects and baseline metabolic syndrome status as covariate.

In the above analyses, the 20 mg rimonabant group was compared with placebo using a modified Bonferroni's procedure (26) to maintain the overall type 1 error rate of 5% because of the multiplicity of doses. All statistical tests were two-sided and used an overall significance level of 5%.

Regression analysis was performed to assess to what extent the observed effects of rimonabant on HDL cholesterol, triglycerides, fasting insulin, HOMA-IR, A1C, and adiponectin in the RIO studies were mediated by change in body weight. The regression analyses presumed that body weight loss has an effect on metabolic variables. To assess any weight-independent effect of rimonabant on a given variable, the portion of the drug's effect that is due to body weight change must be removed from the total effect on the variable. The analysis of the direct effect of rimonabant was based on a standard regression method in which the body weight loss was introduced as a pos-trandomization covariate (ANCOVA). For change in HDL cholesterol and triglycerides at 1 year, the regression analysis was performed on pooled data from all four RIO studies. For fasting insulin and HOMA-IR, the 1-year analysis was performed on the pooled data from the three studies in nondiabetic patients (RIO-Europe, RIO-Lipids, and RIO-North America).

The relationship between weight loss strata, i.e., patients were stratified according to weight lost (≤2 or >2 kg) during the run-in period, and efficacy parameters in the nondiabetic population was examined using a two-way ANOVA model including terms for treatment, weight loss stratum, and their interaction.

Table 1—*Patient disposition, demographics at screening, and baseline values in pooled patients without and with diabetes*

	Without diabetes		With diabetes	
	Placebo	20 mg rimonabant	Placebo	20 mg rimonabant
Patient disposition				
Randomly assigned to treatment	1,255 (100)	2,168 (100)	348 (100)	339 (100)
Safety population (randomized and exposed)	1,254 (99.9)	2,164 (99.8)	348 (100)	339 (100)
ITT	1,254 (99.9)	2,164 (99.8)	348 (100)	339 (100)
Completers	701 (55.9)	1,257 (58.0)	231 (66.4)	229 (67.6)
Discontinued in year 1	554 (44.1)	911 (42.0)	117 (33.6)	110 (32.4)
Lack of efficacy	43 (3.4)	45 (2.1)	5 (1.4)	1 (0.3)
Adverse events	109 (8.7)	317 (14.6)	21 (6.0)	55 (16.2)
Poor compliance	43 (3.4)	74 (3.4)	23 (6.6)	12 (3.5)
Patient's request	283 (22.4)	360 (16.6)	44 (12.6)	30 (8.8)
Lost to follow-up	76 (6.1)	107 (4.9)	18 (5.2)	4 (1.2)
Other (including recovery)	0 (0)	8 (0.3)	6(1.7)	8 (2.4)
Patient demographics at screening				
Sex (M/F) (%)	25.4/74.6	22.4/77.6	45.7/54.3	49.6/50.4
Race				
White	1135 (90.5)	1,916 (88.5)	308 (88.5)	302 (89.1)
Black	78 (6.2)	173 (8.0)	18 (5.2)	19 (5.6)
Current smokers	185 (14.8)	273 (12.6)	51 (14.7)	30 (8.8)
Hypertension	360 (28.7)	721 (33.3)	206 (59.2)	216 (63.7)
Dyslipidemia	919 (73.3)	1,450 (67.0)	186 (53.4)	193 (56.9)
Age [mean (range)] (years)	45.4 (18-77)	45.8 (18-79)	54.8 (28-70)	56.0 (18-70)
Baseline values				
BMI (kg/m^2)	35.9 ± 5.9	36.3 ± 5.9	33.7 ± 3.6	33.6 ± 3.6
Weight (kg)	100.9 ± 20.1	101.1 ± 19.6	96.0 ± 15.1	95.7 ± 14.2
Waist circumference (cm)	106.3 ± 13.8	105.9 ± 14.3	109.1 ± 11.6	108.6 ± 10.1

Data are *n* (%) or means ± SD unless otherwise indicated.

Results

In total, 3,165 (56.7%) of the 5,580 patients in the pooled nondiabetic ITT efficacy dataset completed 1 year of treatment and 692 (66.2%) of 1,045 ITT patients in RIO-Diabetes. The proportions of discontinuations (Table 1) were similar across treatment groups. Although most commonly attributed to patient request, adverse events were more frequently cited as the reason for discontinuation in the 20 mg rimonabant treatment group. Withdrawal of consent (280 [37%]) and failure to meet inclusion or exclusion criteria (195 [26%]) were the predominant reasons for failure of 758 patients to progress from run-in to randomization. At baseline, the three treatment groups were well matched for body weight, BMI, and waist circumference, as well as for age, sex, and race (Table 1). The prevalence of hypertension was slightly lower in the placebo versus 20 mg group (28.7 vs. 33.3%, respectively), and the prevalence of dys-lipidemia was slightly greater (73.3 vs. 67.0%, respectively).

Efficacy outcomes

Run-in period: effect of a hypocaloric diet and promotion of physical activity.

Mean weight and waist circumference, fasting insulin, insulin resistance, LDL cholesterol, and triglycerides all improved slightly during the run-in (Fig. 1), as did BP and A1C (RIO-Diabetes). There was very little change in fasting glucose and total cholesterol-to-HDL cholesterol ratio, whereas HDL cholesterol levels worsened slightly (Fig. 1), as is typical during the early phase of a restricted diet regimen (27).

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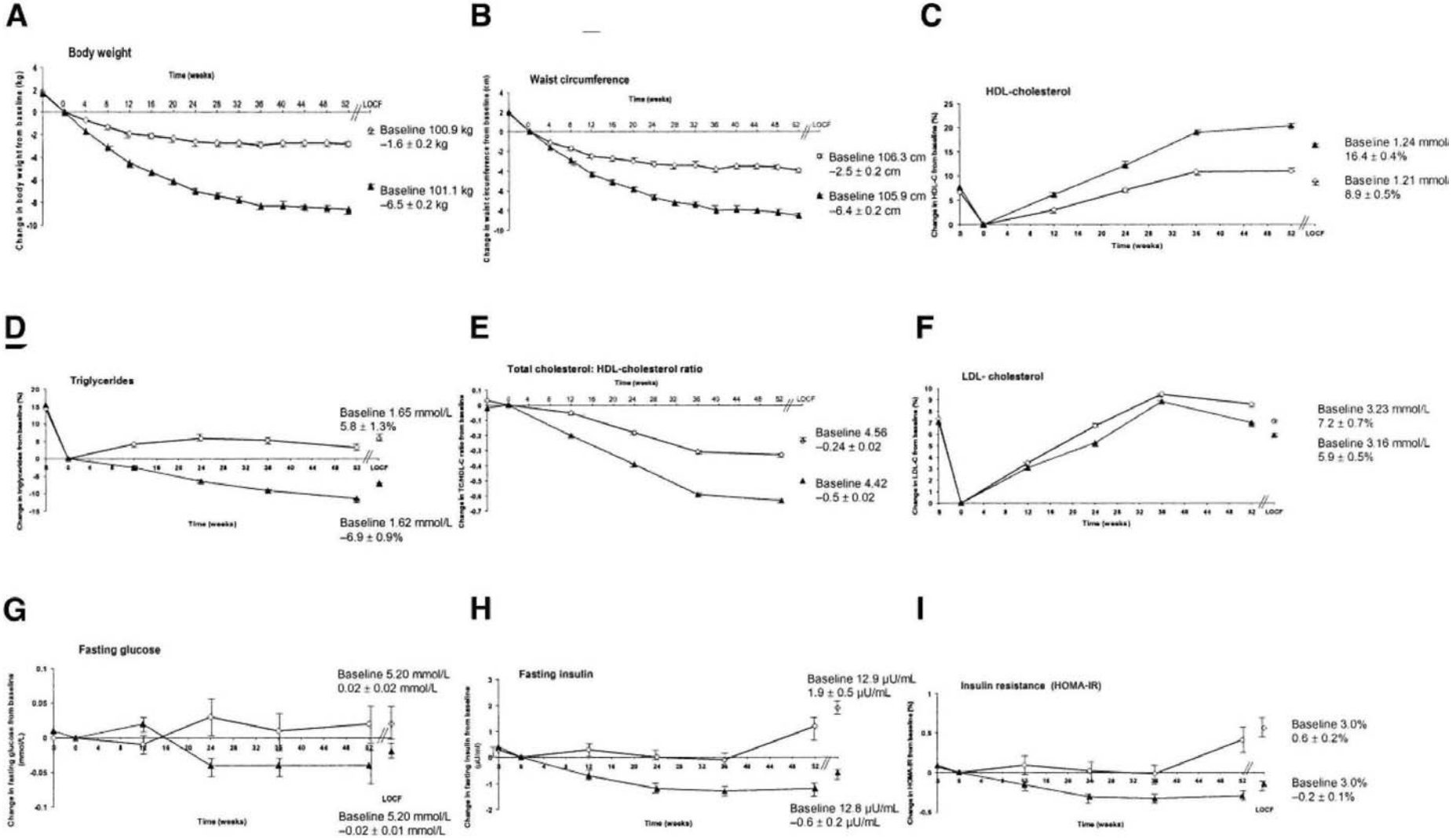
Figure 1—Mean change during run-in (before visit 0) and from baseline (visit 0) (± SE) in body weight (A), waist circumference (B), HDL cholesterol (C), triglycerides (D), total cholesterol (TC)-to-HDL cholesterol (HDL-C) ratio (E), LDL cholesterol (LDL-C) (F), fasting glucose (G), fasting insulin (H), and insulin resistance (HOMA-IR) (I) in a pooled nondiabetic population during 1 year of treatment with 20 mg rimonabant or placebo (ITT population, last observation carried forward [LOCF]). S, screening visit. ◊, Placebo; ▲, 20 mg rimonabant.



Improvements in body weight, waist circumference, and lipid profile.

Loss of body weight in the pooled nondiabetic ITT population after 1 year of treatment was greater in the 20 mg rimonabant group than in the placebo group ($P < 0.001$; Fig. 1). The proportion of patients who lost at least 5% of baseline body weight was 50.8% in the 20 mg rimonabant group, but only 19.7% in patients on placebo ($P < 0.001$). More than one-quarter of patients (27.0%) in the 20 mg rimonabant group lost at least 10% of their body weight compared with only 7.8% of those in the placebo group ($P < 0.001$). Similarly, mean reduction in waist circumference was significantly greater in those receiving 20 mg rimonabant (6.4 cm) than in those given placebo (2.5 cm; $P < 0.001$; Fig. 1).

Patients who received rimonabant also showed statistically significant improvements compared with placebo in lipid parameters (Fig. 1). The increase from baseline in HDL cholesterol and the reductions in triglycerides and the total cholesterol-to-HDL cholesterol ratio were greater in those treated with 20 mg rimonabant than in those receiving placebo ($P < 0.001$). Previously reported results from a regression analysis of data from the four pooled RIO studies showed that 45 and 46% of the treatment effect of rimonabant on HDL cholesterol and triglycerides, respectively, was not attributable to weight loss (Table 2) (28). Overall, LDL cholesterol levels remained unchanged.

Analysis of the effect of certain demographic characteristics on the response to treatment showed significant interactions for some subgroups. Notably, while significant and clinically meaningful weight loss, together with improvements in HDL cholesterol, were observed in both white and black patients, these were greater in white subjects than in black subjects. There was no consistent interaction between any other demographic characteristic (e.g., age, sex, and smoking status) and the response to 20 mg rimonabant (relative to placebo).

Table 2—*Summary of results for primary analysis of metabolic variables after 1 year of treatment with 20 mg rimonabant or placebo with and without adjustment for body weight loss*

	Change from baseline (mean ± SD)				% of overall effect not explained by weight (β/βi)
	Rimonabant 20 mg	Placebo	Overall treatment effect (β_1) (*P* value)	Effect independent of weight loss (β) (*P* value)	
HDL cholesterol (% change)*	16.2 ± 19.1	8.5 ± 16.0	8.0 ± 0.6 (<0.001)	3.6 ± 0.6 (<0.001)	45
Triglycerides (% change)*	-7.2 ± 39.5	6.1 ± 43.0	-14.0 ± 1.4 (<0.001)	-6.5 ± 1.4 (<0.001)	46
Fasting insulin (μIU/ml)†	-0.6 ± 10.5	1.9 ± 15.7	-2.74 ± 0.48 (<0.001)	-1.34 ± 0.51 (0.018)	49
HOMA-IR†	-0.2 ± 2.9	0.6 ± 4.9	-0.76 ± 0.14 (<0.001)	-0.37 ± 0.15 (0.015)	49
A1C (%)‡	-0.6 ± 0.8	0.1 ± 1.0	-0.67 ± 0.07 (<0.001)	-0.37 ± 0.07 (<0.001)	55
Adiponectin (μg/ml)§	2.2 ± 2.5	0.7 ± 1.9	1.5 ± 0.2 (<0.001)	0.85 ± 0.21 (<0.001)	57

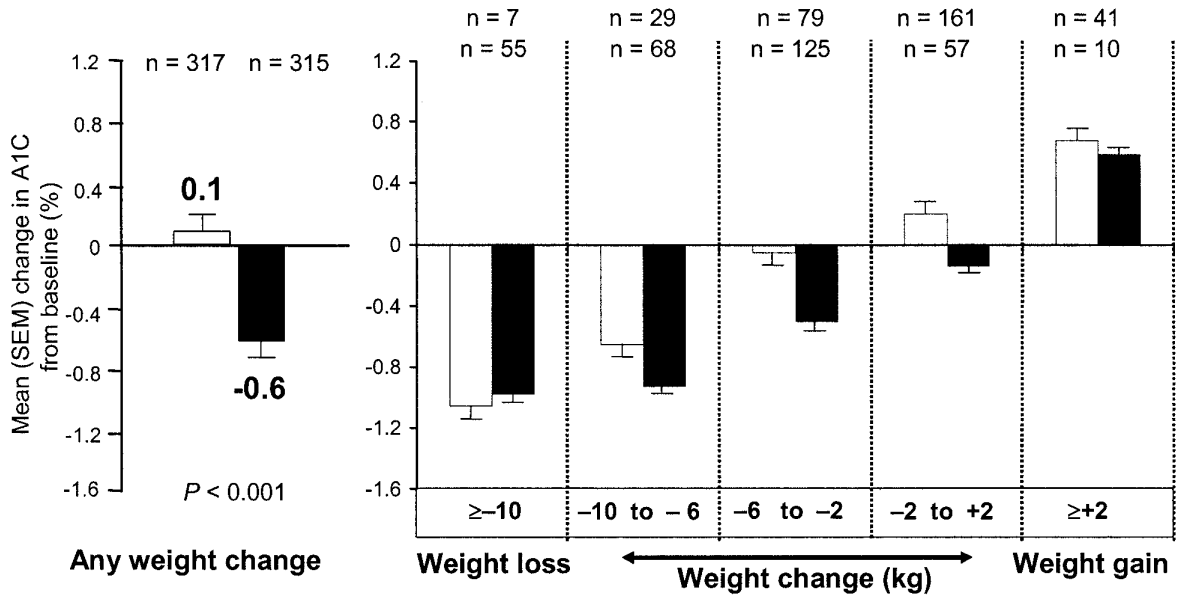
Data for treatment effect are placebo-subtracted means ± SE, with P values for the difference between rimonabant and placebo in parentheses (see text for explanation of how the terms β and βj were derived) (28). *Effects shown are expressed as % change from baseline; data taken from RIO-Lipids, RIO-Europe, RIO-North America, and RIO-Diabetes. †From RIO-North America, RIO-Europe, and RIO-Lipids (nondiabetic patients). ‡From RIO-Diabetes. §From RIO-Lipids.

Improvements in glycemie parameters and adiponectin.

In the RIO-Diabetes study, 20 mg rimonabant produced a significantly greater reduction in A1C than placebo (-0.6 versus + 0.1%, respectively; $P < 0.0001$). The treatment difference of -0.7% A1C was notable given the relatively low baseline of 7.3%. Rimonabant also significantly reduced A1C levels in patients with elevated A1C at baseline (≥8.0%) compared with placebo (-1.1 vs. -0.3%, respectively; $P \leq 0.001$) (29). The placebo-subtracted reduction in A1C in the overall group was still clinically significant after adjustment for body weight loss, and regression analysis showed that 55% of the treatment effect of rimonabant on A1C was beyond that expected from weight loss alone in patients with diabetes (Table 2) (28). Mean change in A1C using categories of body weight changes showed improved A1C levels relative to placebo in all categories except in patients who lost > 10 kg (Fig. 2).

In the pooled nondiabetic efficacy ITT population, both mean fasting insulin and insulin resistance (HOMA-IR) decreased with 20 mg rimonabant and increased with placebo ($P < 0.001$ for intergroup difference; Fig. 1). Regression analysis demonstrated that 49% of these effects were not attributable to weight loss (Table 2) (28). The same pattern of change was seen for mean fasting glucose, and although absolute changes from baseline were small, the difference between the 20 mg rimonabant and placebo groups was statistically significant ($P = 0.034$).

***Figure 2**—Mean change in A1C (± SE) across weight change categories in patients with diabetes from the RIO-Diabetes study ITT LOCF (last observation carried forward) population. □, Placebo; ■. 20 mg rimonabant.*



Although not included in the pooled analysis, it is of interest to report the change from baseline in adiponectin, as observed in the ITT population of the RIO-Lipids study. At 1 year of treatment with 20 mg rimonabant, adiponectin levels were increased by 46.2% ($P < 0.001$ vs. placebo). Regression analysis showed that 57% of the 1-year treatment effect for adiponectin was not attributable to weight loss (Table 2) (28).

In the pooled nondiabetic ITT population, the prevalence of metabolic syndrome in the 20 mg rimonabant group was reduced from 39.8% at baseline to 21.5% at 1 year and to a greater degree than in the placebo group (from 39.3% at baseline to 33.0% at 1 year), the reduction from baseline being significant for 20 mg rimonabant versus placebo ($P < 0.001$). Among patients with metabolic syndrome at baseline, 59.4% of patients improved their metabolic syndrome status with 20 mg rimonabant at 1 year vs. 40.7% of patients in the placebo group ($P < 0.001$). In patients receiving 20 mg rimonabant, baseline systolic (123.7 mmHg) and dia-stolic (78.3 mmHg) BPs were slightly reduced at 1 year (by -0.8 and -0.7 mmHg, respectively); in the placebo group, baseline systolic (123.6 mmHg) and diastolic (78.5 mmHg) BPs were almost unchanged (reduction of -0.1 and -0.2 mmHg, respectively). At study entry (screening), 33.3% ($n = 721$) of patients in the 20 mg rimonabant group and 28.7% ($n = 360$) of patients in the placebo group had hypertension (Table 1), of whom 65.0% ($n = 469$) and 63.4% ($n = 227$) were receiving treatment, respectively. In a subgroup of patients from the pooled nondiabetic ITT population with moderate hypertension (≥140/90 mmHg) at baseline, more pronounced changes in BP were observed. In patients receiving 20 mg rimonabant for 1 year, changes in baseline systolic (143.1 mmHg) and diastolic (88.6 mmHg) BPs were -8.5 and -5.6 mmHg, respectively; in the placebo group, changes in baseline systolic (142.7 mmHg) and diastolic (88.0 mmHg) BPs were -6.9 and -3.5 mmHg, respectively. The reduction in diastolic BP in this subgroup with rimonabant was significant versus placebo ($P = 0.009$). These BP changes are directly due to weight loss (30) and, while they may appear modest, it is noteworthy that they occurred after a significant BP reduction already observed during the run-in period before randomization.

Relationship between prerandomiza-tion weight loss stratum and efficacy end points.

In the nondiabetic population, no significant interactions were observed between weight loss strata (i.e., ≤2 or > 2 kg lost during the run-in period) and treatment at 1 year for waist circumference, lipid parameters, fasting glucose, or insulin resistance. A statistically significant interaction was observed for fasting insulin ($P = 0.018$). In the placebo group, fasting insulin increased more in patients who lost ≤2 kg during run-in compared with patients who lost >2 kg. In the 20 mg rimonabant group, fasting insulin decreased more in patients who lost ≤2 kg during the run-in period.

Although there was no significant interaction between treatment and preran-domization weight loss stratum, postrandomization HDL cholesterol increases were slightly greater in patients who lost >2 kg body weight during the run-in period (placebo 12.9%; 20 mg rimonabant 21.5%) compared with those who lost ≤2 kg (placebo 5.7%; 20 mg rimonabant 12.2%).

Similar differences in HDL cholesterol at 1 year between placebo and 20 mg rimonabant were observed for nondiabetic patients whose HDL cholesterol levels decreased or did not change during the run-in period and those whose HDL cholesterol levels increased during the run-in (7.4 vs. 8.2%, respectively).

Tolerability and safety (pooled analysis of all four RIO studies)

Although reported by a large majority of patients, adverse events generally occurred within the first few months of study treatment and were generally mild and transient. In total, 13.8% of patients receiving 20 mg rimonabant discontinued treatment due to adverse events versus 7.2% receiving placebo (Table 3).

Table 3—*Summary of adverse events after 1 year of treatment with 20 mg rimonabant or placebo*

	Placebo (*n* = 1,602)	20 mg rimonabant (*n* = 2,503)
Summary of adverse events at 1 year (pooled data from four RIO studies)		
Patients with any adverse event	1,310 (81.8)	2,152 (86.0)
Patients with any serious adverse event	67 (4.2)	148 (5.9)
Discontinuations due to adverse events	115 (7.2)	346 (13.8)
Most common adverse events that led to discontinuation*		
Any class, any event	115 (7.2)	346 (13.8)
Depressive disorders†	13 (0.8)	48 (1.9)
Nausea	2 (0.1)	34 (1.4)
Mood alterations with depressive symptoms‡	9 (0.6)	26 (1.0)
Anxiety	5 (0.3)	26 (1.0)
Dizziness	1 (<0.1)	17 (0.7)
Pregnancy	0 (0)	5 (0.5)
Adverse events (by system organ class and preferred term) occurring in ≥2% of patients in the 20 mg rimonabant group and by ≥ 1% compared with patients in the placebo group		
Gastrointestinal disorders	419 (26.2)	761 (30.4)
Nausea	79 (4.9)	299 (11.9)
Diarrhea	77 (4.8)	157 (6.3)
Vomiting	36 (2.2)	100 (4.0)
Nervous system disorders	360 (22.5)	643 (25.7)
Dizziness	79 (4.9)	187 (7.5)
Hypoesthia	9 (0.6)	40 (1.6)
Psychiatric disorders	217 (13.5)	622 (24.9)
Anxiety	39 (2.4)	140 (5.6)
Insomnia	51 (3.2)	134 (5.4)
Mood alterations with depressive symptoms	49 (3.1)	119 (4.8)
Depressive disorders	25 (1.6)	79 (3.2)
Irritability	9 (0.6)	48 (1.9)
Nervousness	4 (0.2)	29 (1.2)
Miscellaneous		
Upper respiratory tract infection	182 (11.4)	311 (12.4)
Asthenia/fatigue	80 (5.0)	151 (6.0)
Contusion	10 (0.6)	54 (2.2)
Tendonitis	16 (1.0)	52 (2.1)
Hot flush	12 (0.7)	47 (1.9)

Data are *n* (%). *Adverse events shown are those that occurred in at least 0.5% of patients in any treatment group (for preferred term), †Includes depression, dysthymic disorder, and major depression according to the Medical Dictionary for Regulatory Activities (MedDRA) : generally more severe than mood alterations with depressive symptoms. ‡Includes anhedonia, depressed mood, tearfulness, and depressive symptoms according to MedDRA: generally less severe than depressive disorders, with more transient symptoms and less therapeutic consequences.

Serious adverse events were uncommon (~5%) and similar across treatment groups (Table 3). In the first year of treatment, the adverse event pattern was similar across relevant patient subgroups, e.g., type 2 diabetes, untreated dyslipidemia, and age >65 years. In particular, depressive disorders, nausea, mood alterations with depressive symptoms, anxiety, and dizziness more frequently led to discontinuation in 20 mg rimonabant-treated patients versus placebo (Table 3). Nausea, dizziness, diarrhea, anxiety, and insomnia were reported more often in the 20 mg rimonabant group versus placebo (Table 3). In the second year of treatment (RIO-North America and RIO-

Europe), the incidence of adverse events (20 mg rimonabant 76.7%; placebo 77.0%) was slightly lower, and incidence of serious adverse events (20 mg rimonabant 4.5%; placebo 5.4%) was similar to that reported in year 1. Adverse events leading to discontinuation were also lower in year 2, with both treatment groups reporting an incidence of 4.7%. No new adverse events were identified during the second year of treatment. Nine deaths were recorded in the pooled safety dataset over 2 years (Table 4). These were evenly distributed between the rimonabant and placebo groups, and no specific patterns were noted; causes of death are described in detail in the articles reporting the original results of each study (17-20).

Although mood alterations with depressive symptoms, depressive disorders, and anxiety events occurred more frequently with rimonabant, their duration, severity, outcomes, and associated Hospital Anxiety and Depression Scale depression subscores were very similar to those with placebo (Table 4). Baseline Hospital Anxiety and Depression Scale depression subscores were normal (≤7) or slightly elevated (8-10) in 91.7 and 6.7% of patients, respectively, and exhibited a similar shift after 1 year in rimonabant and placebo patients. Six patients in the 20 mg rimonabant group reported depressive disorders as serious adverse events. Among them, four patients had a past history of depressive or anxiety symptoms (three of these patients also had contributory stress from work or home life), and five of the six patients recovered after rimonabant was discontinued and corrective treatment was initiated; for the sixth patient, the environmental stressor continued (Table 5).

To evaluate the risk of suicidality, the sponsor performed a specific retrospective analysis of suicidality, which included any case of suicide, suicide attempt, or suicide ideation reported as adverse events, or as associated symptoms of any psychiatric adverse event. One death was reported by the investigator and sponsor in the 5 mg rimonabant group as a completed suicide; however, after the independent blinded assessment of suicidality risk conducted by Columbia Classification Algorithm of Suicide Assessment (C-CASA) (31), as described below, it was concluded that there was not enough information to classify this death as a "completed suicide" (Table 6) (25). The Columbia Classification Algorithm of Suicide Assessment is recommended by the Food and Drug Administration for the assessment of suicide risk and comprises nine categories: 1) completed suicide; 2) suicide attempt; 3) preparatory acts toward imminent suicide behavior; 4) suicidal ideation; 5) self-injurious behavior, intent unknown; 6) not enough information (fatal); 7) self-injurious behavior, no suicidal intent; 8) other (accident, psychiatric, medical); and 9) not enough information (nonfatal). An evaluation of "definitely suicidal behavior/ideation" (categories 1-4) in the four pooled RIO studies showed there were no completed suicides (category 1), suicide attempts (category 2), or preparatory acts toward imminent suicide (category 3) in any of the treatment groups (Table 6). The frequency of suicidal ideation (category 4) in the RIO studies for 20 mg rimonabant and placebo groups was 0.68 and 0.50%, respectively. Suicidal behavior/ideation (categories 1-4) in the RIO studies showed a similar trend to that observed in completed Phase II and Phase III studies by March 2007 for all indications (0.61 and 0.62% for 20 mg rimonabant versus placebo, respectively) and for those studies with obesity and diabetes indications (0.65 and 0.36% for 20 mg rimonabant versus placebo, respectively) (25). An independent blinded review of the frequency of seizures in the completed studies was conducted by neurology experts; seizures were assessed in patient-years because of the rare nature of these events. The frequency of "likely" or "possible" seizures, as defined by the experts, in all completed studies was similar (0.17% per 100 patient-years) in both the 20 mg rimonabant and placebo groups (25).

In the RIO program, no clinically relevant changes in heart rate or QT interval were evident, suggesting that rimonabant had no effect on cardiac repolarization. Laboratory assessments, including hematology, and hepatic and renal function, were similar across treatment groups, except for improvements with 20 mg rimonabant versus placebo in blood levels of uric acid (-24.77 vs. -4.83 μmol/l; $P < 0.001$) and alanine aminotransferase (-5 vs. -1 UI/l; $P < 0.001$). Treatment discontinuations due to laboratory abnormalities were reported rarely and at a similar frequency across treatment groups.

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Table 4—*Causes of death and analysis of patients reporting depressive symptoms, depressive disorders, and anxiety in the* RIO *trial program*

	Run-in	Placebo (*n* = 1,602)	5 mg rimonabant (*n* = 2,520)	20 mg rimonabant (*n* = 2,503)
Causes of death in the RIO program (pooled data from four RIO studies with a maximum duration of 2 years)				
Cardiac failure	—	—	—	1
Coronary artery diseases	—	—	—	1
Cardiac arrest	1	—	1	—
Road traffic accident (non-driver)	—	—	—	1
Uterine adenocarcinoma	—	—	—	1*
Septic shock	—	—	1	—
Hemorrhagic cerebrovascular accident	—	1	—	—
Completed suicide†	—	—	1	—
		Placebo		20 mg rimonabant
Mood alterations with depressive symptoms at 1 year (pooled data from four RIO studies)				
Frequency		49/1,602 (3.1)		119/2,503 (4.8)
Serious events		0		0
Median duration (days)		62		61
Corrective treatment		13/49 (26.5)		33/119 (27.7)
Discontinuation		10/49 (20.4)		34/119 (28.6)
Outcome ‡		41/49 (83.7)		100/119 (84)
Change from baseline in HAD Scale subscore				
Mean ± SD		2.4 ± 4.5		1.9 ± 4.4
Minimum and maximum		(-5, 14)		(-6, 16)
Depressive disorders at 1 year (pooled data from four RIO studies)				
Frequency		25/1,602 (1.6)		79/2,503 (3.2)
Serious events		1/25 (4)		6/79 (7.6)
Median duration (days)		88		69
Corrective treatment		19/25 (76)		57/79 (72.2)
Discontinuation		16/25 (64)		51/79 (64.6)
Outcome***		13/25 (52)		52/79 (65.8)
Change from baseline in HAD Scale subscore				
Mean ± SD		3.6 ± 3.5		3.0 ± 4.7
Minimum and maximum		(-1,11)		(-6, 15)
Anxiety at 1 year (pooled data from four RIO studies)				
Frequency		39/1,602 (2.4)		140/2,503 (5.6)
Serious events		0		0
Median duration (days)		36		31
Corrective treatment		24/39 (61.5)		67/140 (47.9)
Discontinuation		5/39 (12.8)		27/140 (19.3)
Outcome***		33/39 (84.6)		121/140 (86.4)
Change from baseline in HAD Scale subscore				
Mean ± SD		1.4 ± 4.4		2.1 ± 4.3
Minimum and maximum		(-6, 14)		(-5, 14)

Data are *n or n* (%) unless otherwise indicated. *Diagnosed 2 months after start of study treatment. There were two deaths during year 2: cerebrovascular accident and pulmonary embolism (both in the placebo group), †In this analysis, the death of one patient by a fatal gunshot wound was recorded as "completed suicide." ‡Proportion who had recovered or were recovering. HAD Scale, Hospital Anxiety and Depression Scale. The HAD Scale consists of 14 items measuring the level of anxiety and depression in two separate subscales. Scale scores range from 0 (no symptoms) to 21 (maximum distress) for both depression and anxiety and is interpreted with the following cut points: 0-7, normal; 8-10, mild disturbance (probable case); ≥11, moderate to mood disturbance (definite case).

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Table 5—*Details of the six patients in the 20 mg rimonabant group who reported depressive disorders as a serious adverse event during 1 year (data from four* RIO *studies)*

Age (years)	Sex	Onset of event (days)	HAD Scale score (baseline/at time of event)	Past medical history	Psychosocial stressors*	Hospitalized/ treated	Study medication discontinued	Outcome
52	F	208	NA/5	Depression and anxiety	No	Yes/Yes	Yes	Recovered
44	F	18	NA/NA	Depression	Yes	Yes/Yes	Yes	Ongoing (environmental stress)
55	F	79 (recurred on day 119)	NA/NA	Anxiety and asthenia	Yes	Yes/Yes	Yes (alter first episode)	Recovered
37	F	139	2/9	Postpartum depression	Yes	Yes/Yes	Yes	Recovered
54	F	92	NA/NA	No depressive disorder	No	No/Yes	Yes	Recovered
44	F	2	NA/3	No depressive disorder	No	No/Yes	Yes	Recovered

*Any stress factors in family or work life considered to have contributed to the event. HAD Scale, Hospital Anxiety and Depression Scale; NA, not applicable.

Table 6—*Categorization of adverse events related to suicidality at 2 years (pooled reports from four* RIO *studies)*

	Placebo (*n* = 1,602)	5 mg rimonabant (*n* = 2,520)	20 mg rimonabant (*n* = 2,503)
C-CASA category			
1. Completed suicide	0 (0)	0 (0)	0 (0)
2. Suicide attempt	0 (0)	0 (0)	0 (0)
3. Preparatory acts towards imminent suicide behavior	0 (0)	0 (0)	0 (0)
4. Suicidal ideation	8 (0.50)	8 (0.32)	17 (0.68)
5. Self-injurious behavior, intent unknown	0 (0)	0 (0)	0 (0)
6. Not enough information (fatal)	0 (0)	1 (0.04)	0 (0)
9. Not enough information (nonfatal)	1 (0.06)	0 (0)	2 (0.08)

Data are n (%). Patients were exposed in the same treatment group during the whole study. Includes information from collection of associated symptoms to depressive events. Data are according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Categories 1-4 represent definitely suicidal behavior/ideation; 5, 6, and 9 represent possible suicidal cases. Categories 7 and 8 (not shown) are self-injurious behavior, no suicidal intent, and other (accident, psychiatric, medical), respectively.

CONCLUSIONS

Global cardio-metabolic risk represents the overall risk of developing type 2 diabetes and/or cardiovascular disease due to a cluster of modifiable risk factors/markers (1). These include classic risk factors such as smoking, high LDL cholesterol levels, hypertension, and elevated blood glucose, in addition to risk factors closely associated with abdominal obesity, such as insulin resistance, low HDL cholesterol levels, and high triglyceride levels and inflammatory markers.

Measurement of cardiometabolic risk factors in this pooled population of overweight and obese patients demonstrated that 1 year of treatment with 20 mg/day rimonabant, in addition to a hypocaloric diet and promotion of physical activity, produced substantial reductions in weight and waist circumference as well as improvements in HDL cholesterol, triglycerides, A1C, fasting glucose and insulin, and insulin resistance, which were significantly superior to the effects of placebo.

In this analysis, most efficacy measures improved noticeably during the run-in period, during which patients received a modestly hypocaloric diet and were encouraged to do more physical exercise. This is consistent with existing guidelines on dieting and exercise advice (32); however, it is notable that while many measures, including weight and waist circumference, continued to improve over the study period in those who continued with this intervention alone (placebo patients), the addition of rimonabant produced better changes in cardiometabolic risk factors than placebo.

The change over time in efficacy measures presented in Fig. 1 showed rimonabant to have a rapid onset of effect. A difference in mean body weight between 20 mg rimonabant and placebo was evident after only 4 weeks of treatment, and a difference in mean waist circumference after 8 weeks. For all other end points except fasting glucose, appreciable differences between active treatment and placebo were seen at the first evaluation after baseline (month 3). Although improvements from baseline in body weight, waist circumference, HDL cholesterol, and triglycerides in the 20 mg rimonabant group continued throughout the study up to the 12-month time point, changes from baseline in fasting glucose, insulin, and HOMA-IR measures reached a maximum by month 6, after which little or no change occurred in this nondiabetic population. In RIO-Diabetes, the reduction in A1C levels continued until month 9 and was sustained to the end of the study.

The presence of comorbidities (e.g., low HDL cholesterol, high triglycerides, or elevated blood glucose) in patients with high waist circumference confers a higher risk of developing heart disease (33,34). All patients without diabetes in this pooled analysis were overweight or obese, and many had comorbidities (dyslipidemia in ~70% and hypertension in ~30%). Nonetheless, improvements were observed in mean HDL cholesterol and triglyceride levels as well as beneficial changes in glucose metabolism in the 20 mg rimonabant group. Similar changes in lipid profiles were seen in patients with diabetes who received rimonabant in the RIO-Diabetes study (20), together with a significant decrease in A1C.

Although rimonabant had no effect on LDL cholesterol in the pooled dataset of patients without diabetes, it should be noted that two of the three component studies included patients with treated dyslipidemia. Improvements in triglycerides and HDL cholesterol with rimonabant were similar in statin-treated and non-statin-treated patients (35). In addition to improving the lipid and glycemic measures reported in this pooled analysis, rimonabant (20 mg/day) was shown to increase adiponectin levels by 46.2% from baseline in the RIO-Lipids study (17). This change, as well as reductions in the levels of plasma leptin and C-reactive protein, were significantly different than placebo responses. Adopting a multifactorial treatment approach to cardiometabolic risk reduction through the addition of an agent such as rimonabant may be a valuable alternative strategy, particularly as patients with abdominal obesity have multiple clustering factors that increase their risk of major cardiovascular events (35).

Analysis of these pooled results according to the degree of weight loss from baseline shows progressively greater improvements in waist circumference, HDL cholesterol, triglycerides, and glycemic measures, with increasing weight loss with all study treatments. Patients in the 20 mg rimonabant group, however, experienced greater improvements in HDL cholesterol and triglycerides than placebo-treated patients with the same degree of weight response. A similar finding was observed for A1C changes in the diabetic population (Fig. 2). Although the numbers of placebo-treated patients achieving weight loss of ≥5% from baseline were relatively small and quite broad categories of weight change were used, these findings support previous observations that a substantial proportion of the improvements in cardiometabolic risk factors produced by rimonabant therapy exceed the levels that would be expected solely from the degree of weight loss, probably reflecting a direct pharmacologie effect of the drug in peripheral tissues (17-20).

As is typical for long-term trials and programs involving weight loss assessments (36), 43% of patients in the pooled efficacy dataset (but only 33% in the diabetic population) withdrew from the study during the treatment period; however, the rate of withdrawal was no different in patients receiving active treatment or placebo.

The analysis of data from all four RIO studies showed rimonabant to be well tolerated, with a similar incidence of adverse events to placebo in the complete pooled dataset. The adverse events occurring more often with rimonabant were in three body systems: gastrointestinal, neurological, and psychiatric. Although the overall discontinuation rates in the rimonabant and placebo groups were very similar, adverse events causing discontinuation were more frequent with rimonabant (most commonly, depressive disorders, nausea, mood alterations with depressive symptoms, anxiety, and dizziness).

Although neurological and psychiatric disorders were more frequent in the 20 mg rimonabant group, the total incidence remained low, and most events were of mild or moderate intensity; the duration, severity, and outcome of these events in this group were also very similar to placebo, suggesting no qualitative difference in this type of event. The change from baseline in Hospital Anxiety and Depression Scale depression subscores at 1 year showed no differences between active treatment and placebo. Rimonabant is associated with a higher incidence of depression compared with placebo. In rare occasions, the clinical picture of depression included suicidal ideations in both treatment groups. Monitoring of vital signs, electrocardiogram, and clinical laboratory tests showed rimonabant to have a similar safety profile to placebo.

Interestingly, a liver function analysis showed that rimonabant reduced alanine aminotransferase levels, a marker of fatty liver disease, demonstrating a potentially beneficial effect of rimonabant on hepatic steatosis. Rimonabant has previously been shown to reduce hepatic steatosis in rodents (37).

The benefit of pooling data from studies with a common design is that the resultant large sample may reveal trends or associations not revealed in the component studies. Other pooled analyses have also been performed to specifically assess the effect of 20 mg rimonabant on BP changes in the four RIO studies (30) and on glucose tolerance in the RIO-Lipids and RIO-Europe studies (38). The results from the present pooled sample agree closely with the findings of the three constituent studies in patients without type 2 diabetes, serving to emphasize the efficacy of rimonabant for modifying cardio-metabolic risk factors (17-19).

The patient population in the pooled efficacy analysis contained few non-white patients (11.1%), which limits the extent to which the findings can be generalized to other ethnic groups. Subgroup analysis showed that ethnicity affected the response to 20 mg rimonabant (relative to placebo). The reason for this is unclear, but could be a result of differences in plasma clearance of rimonabant in different ethnic groups.

In conclusion, treatment with the first selective CB_X blocker rimonabant was associated with clinically meaningful weight loss, a reduction in abdominal obesity (as measured by waist circumference), and improvements in insulin resistance, lipid profile, and glucose metabolism in a large population of at-risk overweight/obese patients. Furthermore, rimonabant was generally well tolerated in the four pooled RIO studies with a defined safety profile. The occurrence of recurrent depression requires special attention. Rimonabant is therefore a potentially effective new treatment for the improvement of multiple cardiometabolic risk factors in patients with abdominal obesity.

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