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

Effects of monotherapy with rimonabant, the first selective CB₁ 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 (ΔA1C −0.51%; P = 0.0002), with a larger rimonabant effect in patients with baseline A1C ≥8.5% (ΔA1C −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-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 (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 type 2 diabetes (14).

Rimonabant, a selective CB₁ 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...
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 diettian at baseline and reinforcement at the 3- and 6-month study visits. Overweight (BMI ≥27 to <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 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.

**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 0.03, 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-

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**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 |
| ≥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 antidysslipemia 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).
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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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 2, poor compliance 1, 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/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 A1C reduction from baseline was significantly greater with rimonabant versus placebo (−0.8 vs. −0.3%, respectively; P = 0.0002) (Table 2, Fig. 1A). 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. 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 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. 1D 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. 1F), 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.

| LDL particle size (Å) | Placebo | 20 mg rimonabant | P value vs. placebo |
|----------------------|---------|------------------|---------------------|
| 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† | --- | −5.53 ± 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.
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.
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 \((\text{BMI} \leq 27 \, \text{kg/m}^2)\), 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 \((2.9 \text{ vs. } 1.4\%, \text{ respectively})\). 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 \((3.6\%)\). 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 CB1 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/m² 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 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-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-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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References
1. Engelgau MM, Geiss LS, Saadiddle JB, Boyle JP, Benjamin SM, Gregg EW, Tierney EF, Rios-Burrows N, Mokdad AH, Ford ES, Imperatore G, Narayan KM: The evolving diabetes burden in the United States. Ann Intern Med 140:945–950, 2004
2. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 21:1414–1431, 1998
3. Huxley R, Barzi F, Woodward M: Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 332:73–78, 2006
4. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229–234, 1998
5. Misra A, Vikram NK: Clinical and pathophysiologic consequences of abdominal adiposity and abdominal adipose tissue deposits. Nutrition 19:457–466, 2003
6. American Diabetes Association: Standards of medical care in diabetes—2008. Diabetes Care 31 (Suppl. 1):S12–S54, 2008
7. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Kim C, Lau J: Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. Arch Intern Med 164:1395–1404, 2004
8. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O’Neill MC, Zinnman B, Viberti G; ADOPT Study Group: Glycemic durability of rosiglitazone, metformin, or glipizide monotherapy. N Engl J Med 355:2427–2443, 2006
9. DeFronzo RA: Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 133:73–74, 2000
10. Rosenstock J, Zinnman B: Dipeptidyl peptidase-4 inhibitors and the management of type 2 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 14:98–107, 2007
11. Amori RE, Lau J, Pittas AG: Efficacy and safety of incretin therapy in type 2 diabe-
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tes: systematic review and meta-analysis. JAMA 298:194–206, 2007
12. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R: The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev 27:73–100, 2006
13. Kakafika AI, Mikhailidis DP, Karagiannis A, Athyros VG: The role of endocannabinoid system blockade in the treatment of the metabolic syndrome. J Clin Pharmacol 47:642–652, 2007
14. Hollander P: Endocannabinoid blockade for improving glycemic control and lipids in patients with type 2 diabetes mellitus. Am J Med 120 (Suppl. 1):S18–S28, 2007
15. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal L, RIO-Diabetes Study Group: Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomized controlled study. Lancet 368:1660–1672, 2006
16. World Health Organization: Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Report of a World Health Organization Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus (WHO/NCD/NCS/99.2). Geneva, World Health Org., 1999
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419, 1985
18. Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M: Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 77:1287–1293, 1993
19. Henry RR, Scheaffer L, Olefsky J: Glycemic effects of intensive caloric restriction and isocaloric refeeding in noninsulin-dependent diabetes mellitus. Am J Clin Nutr 61:917–925, 1995
20. Liu YL, Connoley IP, Wilson CA, Stock MJ: Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lepavan/Lepob mice. Int J Obes (Lond) 29:183–187, 2005
21. Gary-Bobo M, Elachouri G, Scatton B, Le Fur G, Oury-Donat F, Soubrie P: The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol 63:908–914, 2003
22. Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, Batkai S, Harvey-White J, Mackie K, Offertaler L, Wang L, Kunos G: Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. J Clin Invest 115:1298–1305, 2005
23. Jbilo O, Ravinet-Trillou C, Arnone M, Buisson I, Bribes E, Pêleraux A, Pénarier G, Soubrié P, Le Fur G, Galiégue S, Caseillas P: The CB1 receptor antagonist rimonabant reverses the diet-induced obesity phenotype through the regulation of lipolysis and energy balance. FASEB J 19:1567–1569, 2005
24. The Look AHEAD Research Group: Reduction in weight and cardiovascular risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diabetes Care 30:1374–1383, 2007
25. Clinical Trials. Available from http://www.clinicaltrials.gov. Accessed 1 May 2008