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Long-term effect of CB_1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study[†]

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Abstract:

Aims : Rimonabant, the first selective cannabinoid type 1 receptor blocker, has been shown to produce weight loss and improvements in several cardiometabolic risk factors over 1 year. We report the 2 year efficacy and tolerability data of rimonabant. **Methods and results :** Patients with a body mass index ≥30 or >27 kg/m^2 with treated/untreated hypertension, dyslipidaemia, or both, were randomized to double-blind treatment with placebo, rimonabant 5 or 20 mg once daily plus a calorie-restricted diet for 2 years. Weight loss from baseline to 2 years in the intention-to-treat population was significantly greater with rimonabant 20 mg (mean ± SD: -5.5 ±7.7 kg; P < 0.001) and 5 mg (-2.9 ± 6.5 kg; P = 0.002) than placebo (-1.2 ± 6.8 kg). Rimonabant 20 mg produced significantly greater improvements than placebo in waist circumference, high-density lipoprotein cholesterol, triglycerides, fasting glucose and insulin levels, insulin resistance, and metabolic syndrome prevalence. Rimonabant 20 mg produced clinically meaningful improvements in all Impact of Weight on Quality of Life-Lite questionnaire domain scores at 2 years. Rimonabant was generally well tolerated and rates of adverse events, including depressed mood disorders and disturbances were similar to placebo during year 2. Proportions of patients with clinically significant depression (Hospital Anxiety and Depression Scale score >11) were similar in all treatment groups. **Conclusion :** Rimonabant 20 mg over 2 years promoted clinically relevant and durable weight loss and improvements in cardiometabolic risk factors.

Keywords: CB_1 receptor · Cardiovascular risk factors · Endocannabinoid system · Overweight · Obesity · Rimonabant

Introduction

Obesity is considered a major cardiovascular risk factor. Rimonabant, the first selective cannabinoid type 1 (CB_1) receptor blocker, represents a new approach to the management of both cardiovascular and metabolic risk factors in overweight and obese patients. The endocannabinoid system (ECS) is involved in regulation of energy homeostasis and the metabolism of lipids and glucose through central and peripheral pathways.[4,5] CB_1 receptors are present in adipose tissue, liver, pancreas, skeletal muscle, the gastrointestinal tract, and various regions of the brain.[5-12] Recent work in animal models has shown that activation or blockade of the ECS produces changes in adiponectin expression, insulin-stimulated glucose disposal, and hepatic lipogenic enzymes, as well as central effects on energy homeostasis.[6-8] The role played by hepatic and pancreatic CB_1 receptors is an evolving field of study, but there is now evidence that overactivity of the ECS is associated with abdominal obesity and type 2 diabetes.[13-15]

Three multicentre, randomized, placebo-controlled trials in non-diabetic and one in diabetic overweight and obese patients in the Rimonabant in Obesity and Related Metabolic Disorders (RIO) programme demonstrated that rimonabant effectively reduced body weight (BW) and abdominal obesity and improved glucose and lipid metabolism after 1 year (RIO-Europe, RIO-Lipids, and RIO-Diabetes) and 2 years (RIO-North America) of treatment.[16-19] Moreover, these effects appeared to be additional to the benefits of a mild hypocaloric diet, and the metabolic improvements after 1 year were approximately twice what would have been expected from the effect of weight loss alone.[16-20] Here, we report 2 year data from the RIO-Europe trial, including additional outcomes not reported at the 1 year stage: oral glucose tolerance data, health-related quality of life (HRQoL),

[†] Clinical Trial Registration No. NCT00386061 http://wwwclinicaltrials.gov/ct/show/NCT00386061?order=1.
[‡] Members are listed in the appendix.

and changes in Hospital Anxiety and Depression Scale (HADS) scores. This trial therefore gives further valuable insights into the long-term efficacy and safety of rimonabant for improving cardio-metabolic risk factors in overweight and obese patients.

Methods

RIO-Europe was a randomized, double-blind, placebo-controlled, parallel group, fixed-dose multicentre study conducted at centres in Europe and the USA. After a 4 week, single-blind, placebo run-in period, patients were randomized to receive placebo, rimonabant 5 mg or 20 mg, double-blinded once daily for 2 years according to a 1:2:2 ratio. Patient recruitment, inclusion and exclusion criteria, screening procedures, treatment interventions, which included a dietary regimen designed to yield an energy deficit of ~600 kcal/day, and assessments have been described previously in the published report of the 1 year results,[16] but are listed briefly in the following sections (further details are provided in the Supplementary material online).

Men and women aged 18 years or older, with a body mass index (BMI) ≥30 kg/m^2, or a BMI >27 kg/m^2 with treated or untreated hypertension and/or dyslipidaemia, who had experienced <5 kg variation in BW during the previous 3 months were eligible to participate. Patients with clinically significant endocrine disease, diabetes mellitus, cardiovascular or pulmonary disease, hepatic and renal disorders, or clinically significant neurological or psychological illness (particularly history of severe depression or history of suicide attempt) were excluded. The trial was conducted in accordance with ethical guidelines and approval procedures.

Patient visits were scheduled every 14 days forthe first month of the study and every 28 days thereafter. BW, waist circumference (WC), and blood pressure (BP) were measured at screening, randomization, and all subsequent visits. Lipid profile, fasting glucose, and insulin were measured every 3 months[21]. Oral glucose tolerance testing (OGTT) was performed at baseline, 1 year, and 2 years, and the prevalence of metabolic syndrome determined at the same time points. Definitions for glucose tolerance, hypertension, and dyslipidaemia have been described previously.[16] Metabolic syndrome was determined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),[22] and in a *post hoc* analysis, according to the more recent International Diabetes Federation (IDF) definition.[23]

Main endpoints assessed at 2 years were changes from baseline in BW, WC, proportion of patients who achieved weight loss ≥5 and ≥10% from baseline BW, HDL-C, triglycerides, fasting glucose and insulin levels, glucose tolerance, and the prevalence of metabolic syndrome. Other endpoints included changes in BP, total cholesterol (TC), LDL-C, and insulin resistance, derived from the homeostasis model assessment of insulin resistance (HOMA-IR).[24]

The Medical Outcomes Study Short-Form (MOS SF-36) and a patient's satisfaction scale were included as exploratory secondary measures, and HRQoL was specifically assessed using the obesity-specific Impact of Weight on Quality of Life (IWQOL-Lite) questionnaire. Assessments were performed at screening, baseline, and every 3 months as described previously. Mood was also evaluated at baseline and every 3 months using HADS scores,[27] higher scores indicating worsening mood. This measurement was included as a protocol amendment after recruitment had commenced. Patients presenting with symptoms of depression or a HADS score ≥11 were to be referred to a psychiatrist for diagnosis and further management. Safety assessments (physical examination, standard laboratory tests, electrocardiogram) were performed every 3 months. Adverse events were recorded at each visit.

Analysis

The 2 year efficacy results were analysed as the changes from baseline to the end of year 2. All variables were secondary efficacy endpoints, and the primary study endpoint defined in the study protocol was weight loss over 1 year.[16] Efficacy analyses of the 2 year data were performed for patients in the intention-to-treat (ITT) population using the last observation carried forward (LOCF) approach to impute missing values at 2 years. The ITT population consisted of all randomized patients who received at least one double-blind dose of study drug, attended at least one post-baseline visit, and had a baseline assessment. Data for the completer population included all patients in the ITT population who completed 2 years' treatment and were analysed using observed data without imputation. Treatment comparisons of rimonabant 20 mg vs. placebo and rimonabant 5 mg vs. placebo were made by analysis of variance (ANOVA) with the modified Bon-ferroni procedure[28] to adjust for multiple comparisons. Significance was claimed at the 0.05 level when the following conditions were met: $P <$ 0.025 for rimonabant 5 or 20 mg vs. placebo; $P < 0.05$ for both comparisons. The ANOVA model included a term for treatment as a fixed effect. The model for weight also included a term for randomization stratum. The

estimates of metabolic responses to treatment that could not be attributed to weight loss alone were based on pre-specified standard regression methodology, in which weight loss (change in weight from baseline to 2 years) was introduced as a covariate (analysis of covariance, ANCOVA), using a previously described statistical model. All results are means ± SD for the ITT population, unless otherwise specified.

Role of the funding source

The study was designed by the Operational Committee, which was composed of the investigators of the RIO programme. Data were collected by the pharmaceutical sponsor and were assessed jointly by the authors and the sponsor. The data were interpreted and the manuscript was written by the authors. The corresponding author had full access to all data and had final responsibility for submission of the paper.

Results

The disposition of patients (n = 1507) over the study period is shown in Supplementary material online, *Figure A*. Overall, the proportion of initially randomized patients who completed the 2 year study was 128/305 patients (42.0%) in the placebo group, 288/603 patients (47.8%) in the rimonabant 5 mg group, and 268/599 patients (44.7%) in the rimonabant 20 mg group.

Baseline characteristics of the treatment groups were similar *(Table 1),* with a mean age of 45.0 (SD 11.5) years and a mean BMI of 36 (SD 5.9) kg/m^2.[16] At baseline, 41% of the patients had hypertension, 61% met the criteria for dyslipidaemia, and 41% met the criteria for metabolic syndrome by NCEP ATP III definition (52% by IDF definition).[16]

BW reduction from baseline to 2 years in the ITT population was significantly greater in both the rimonabant 5 and 20 mg groups than in the placebo group *(Figure 1A; Table 2).* In the rimonabant 20 mg group, the placebo-subtracted BW loss after 2 years of treatment [-4.2 kg (standard error of the mean SE 0.5 kg)] was similar to that observed after 1 year of treatment [-4.7 kg (SE 0.4 kg)]. A significantly greater proportion of the ITT population treated with rimonabant lost ≥5% of baseline weight than did those in the placebo group during years 1 and 2: 44.4% (264/ 595) in the rimonabant 20 mg and 29.8% (178/597) in the rimonabant 5 mg vs. 15.6% (47/302) in the placebo group; both P < 0.001 vs. placebo. A greater proportion of patients receiving rimonabant 5 and 20 mg also achieved ≥10% weight loss compared with placebo: 11.2% (67/597) and 22.0% (131/595) vs. 6.3% (19/302), respectively; P = 0.026 and P < 0.001 vs. placebo, respectively.

Rimonabant 20 mg treatment reduced WC significantly more than placebo: -5.7 cm (SE 0.3 cm) vs. -1.8 cm (SE 0.4 cm); P < 0.001 (Figure *1B* and *Table 2).* In the rimonabant 20 mg group, the placebo-subtracted WC after 2 years of treatment [-3.9 cm (SE 0.5 cm)] was similar to that observed after 1 year of treatment [-4.2 cm (SE 0.5 cm)].

HDL-C levels increased to a greater extent between baseline and the 2 year follow-up in both rimonabant 5 and 20 mg groups compared with the placebo group *(Table 2).* Treatment with rimonabant 20 mg significantly increased HDL-C and decreased triglycerides from baseline by 22.6 and 4.1%, respectively [P < 0.001 (per cent change from baseline data) vs. placebo for both] in the ITT population *(Figure 1C).* TC was increased by 2.5% from baseline with rimonabant 20 mg vs. 1.9% with rimonabant 5 mg and 1.6% with placebo. LDL-C was increased by a comparable extent by each treatment compared with baseline (6.8, 7.2, and 7.0% for rimonabant 20 mg, rimonabant 5 mg, and placebo, respectively). Furthermore, HDL-C increased significantly with rimonabant 20 mg vs. placebo in patients with low HDL-C at baseline (by 8.1% in year 1 and 10.8% in year 2 in patients without hypertriglyceridaemia; P < 0.001 vs. placebo for both, and by 8.4% in year 1 (P < 0.05 vs. placebo) and 9.3% in year 2 in patients with hypertriglyceridaemia (triglycerides ≥ 1.69 mmol/L); P < 0.01 vs. placebo].

The proportion of patients who had hypertriglyceridaemia at 2 years was lower than at baseline in the rimonabant 20 mg group (27.9% at baseline; 18.2% at 2 years), whereas in the placebo group, the proportion increased slightly (from 26.8% at baseline to 28.6% at 2 years).

Interestingly, the increases in HDL-C levels in the rimonabant 20 mg group were greater than predicted from the level of weight loss observed. Regression analysis showed that approximately half of the effect of rimonabant 20 mg on HDL-C and triglyceride levels at 2 years (relative to placebo) was found to be unattributable to weight loss. For the change in HDL-C, the total placebo-subtracted increase from baseline was 10%, and the amount unattributable to weight loss was 5.7% (P < 0.001). Similarly for triglycerides, the total placebo-subtracted

decrease was -14% *(Figure 1D),* and the change unattributable to weight loss was -7.9% ($P = 0.012$). Furthermore, analysis of changes in HDL-C and triglycerides by weight loss category at 2 years indicated numerically greater improvements for patients receiving rimonabant 20 mg than for those receiving placebo irrespective of weight loss, except for patients whose weight decreased by ≥10 kg *(Figure 2A* and *B*).

Table I: *Baseline characteristics of the treatment groups*

Characteristic	**Year 1**			**Year 2**		
	Placebo, (*n* = 305)	**Rimonabant 5 mg, (*n* = 603)**	**Rimonabant 20 mg, (*n* = 599)**	**Placebo, (*n* = 168)**	**Rimonabant 5 mg, (*n* = 363)**	**Rimonabant 20 mg, (*n* = 355)**
Age[3], years	45.0(11.6)	45.4(11.2)	44.6 (11.9)	47.4(11.1)	46.7(11.2)	45.5 (11.3)
Gender (female), *n* (%)	244 (80.0)	476 (78.9)	478 (79.8)	132(78.6)	278 (76.6)	267 (75.2)
Caucasian, *n* (%)	290 (95.1)	565 (93.7)	555 (92.7)	160(95.2)	345 (95.0)	332 (93.5)
BMI[a], kg/m^2	36.3 (5.9)	36.6 (6.0)	36.8 (5.9)	36.3 (6.2)	36.5 (5.7)	36.8 (5.9)
Hypertension, *n* (%)	116 (38.0)	264 (43.8)	237 (39.6)	77 (45.8)	170 (46.8)	154 (43.4)
Dyslipidaemia, *n* (%)	189 (62.0)	371 (61.5)	355 (59.3)	102(60.7)	231 (63.6)	215 (60.6)
Current smokers, *n* (%)	60(19.7)	136(22.6)	102(17.0)	29(17.3)	79 (21.8)	61 (17.2)
Weight[a], kg	100.0(20.3)	100.9(19.8)	101.7(19.5)	101.2(19.9)	102.4 (20.1)	104.1 (20.2)
Waist[a], cm	107.7(13.8)	108.4(14.3)	108.8(14.1)	110.6(14.6)	110.9 (14.4)	110.9 (14.7)
TC[a], mmol/L	5.30(1.00)	5.36 (0.95)	5.36 (0.99)	5.32(1.03)	5.39 (0.95)	5.32 (0.96)
HDL-C[a], mmol/L	1.26 (0.34)	1.27(0.33)	1.27 (0.33)	1.27 (0.35)	1.26(0.31)	1.27(0.33)
TG[a], mmol/L	1.47(0.87)	1.46(0.91)	1.44 (0.85)	1.43 (0.87)	1.44(0.86)	1.44(0.80)
LDL-C[a], mmol/L	3.14 (0.82)	3.19(0.77)	3.20 (0.80)	3.16(0.82)	3.23 (0.78)	3.17(0.80)
TCHDL-C ratio[a]	4.44(1.28)	4.44(1.24)	4.42(1.21)	4.46(1.32)	4.50(1.26)	4.42 (1.20)
Non-HDL-C mmol/L	4.04 (0.99)	4.09 (0.93)	4.09 (0.97)	4.07 (0.99)	4.13 (0.94)	4.06 (0.95)
Fasting glucose[a], mmol/L	5.3 (0.70)	5.30 (0.60)	5.3 (0.70)	5.3 (0.8)	5.4 (0.6)	5.3 (0.7)
Fasting insulin[a], µlU/mL	12.5 (9.4)	12.8(9.2)	13.0(9.5)	11.7(6.8)	12.7(10.4)	12.8 (10.1)
HOMA-IR[a]	3.0 (2.6)	3.1 (2.8)	3.1 (2.5)	2.8 (1.8)	3.1 (3.3)	3.1 (2.7)
SBP[a], mmHg	126.8(13.7)	127.0(14.8)	127.1 (14.1)	127.2(14.0)	127.3 (14.7)	127.9 (14.1)
DBP[a], mmHg	79.7 (8.5)	79.6 (9.1)	79.5 (8.8)	80.3 (8.1)	79.7 (9.3)	79.8 (8.9)

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides. [a]Data are presented as mean (SD).

After 2 years, reductions in both fasting glucose and insulin levels were significantly greater with rimonabant 20 mg than with placebo *(Table* 2). The benefits of rimonabant for improving insulin resistance also remained evident at 2 years, with a significant advantage over placebo for both rimonabant doses. Glucose tolerance also improved; the mean OGTT 30 min post-load plasma glucose concentration was lower at 2 years than at baseline in the rimonabant 20 mg group but unchanged with placebo (ITT; P = 0.005 for treatment difference); the same trend, although not significant, was observed for the mean OGTT 120 min post-load plasma glucose level (Supplementary material online, *Table A).* Similarly, the OGTT insulin response was significantly lower with rimonabant 20 mg than with placebo at 2 years ($P = 0.014$ and P = 0.006 for 30 and 120 min post-load, respectively) (Supplementary material online, *Table A).* In accordance with these results, reductions in mean area under curve values (0-120 min) for OGTT glucose and insulin were significantly greater with rimonabant 20 mg than with placebo ($P = 0.002$ and $P < 0.001$, respectively) *(Table 2).* Furthermore, the distribution of patients classified as NGT, IGT, and DGT at 2 years differed between treatment groups, with a greater proportion of NGT patients in the rimonabant 20 mg group (90.7%) than in the placebo group (83.0%; $P = 0.001$) (IGT and DGT proportions: 8.8 and 0.5%, rimonabant 20 mg; 12.9 and 4.1%, placebo). Proportionally, more patients with IGT at baseline improved to NGT at 2 years with rimonabant 20 mg than with placebo [36/50 (72.0%) vs. 12/22 (54.5%); $P = 0.040$], SBP and DBP were reduced following 2 years of rimonabant 20 mg treatment *(Table* 2), although the changes were not significantly different from placebo. Reductions from baseline were also seen in patients who had a diagnosis of hypertension at baseline, but mean changes in the rimonabant 20 mg group at 2 years [-1.4 mmHg (SD 13.8) and -1.9 mmHg (SD 8.9) for SBP and DBP, respectively] were not significantly different to placebo.

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At the 2 year follow-up, significantly fewer patients in the rimonabant 20 mg group than in the placebo group met the criteria for metabolic syndrome (by NCEP ATP III definition, 21.5 vs. 32.1%, $P < 0.001$; by IDF definition, 34.8 vs. 42.9%, $P = 0.008$).

A number of exploratory secondary parameters were investigated: (i) SF-36: a significantly greater improvement was observed only in physical functioning at 1 year[16] and 2 years ($P = 0.013$) in the rimonabant 20 mg group compared with placebo; (ii) patient's satisfaction scale: significantly more patients on rimonabant 20 mg were 'very' or 'exceptionally' satisfied at 1 year and 2 years compared with patients on placebo; (ii) IWQOL-Lite: significantly greater improvement with rimonabant 20 mg in HRQoL in the physical function domain at 1 year[16] and 2 years ($P = 0.002$ vs. placebo); and IWQOL-Lite total score: significant improvement was observed in the rimonabant 20 mg group compared with placebo at 1 year[16] and 2 years ($P = 0.021$ vs. placebo).

Figure I: *Change from baseline in (A) body weight and (β) waist circumference. Per cent change from baseline in (C) high-density lipoprotein cholesterol and (D) triglycerides. Data are mean (SE) values for patients completing each scheduled visit, with additional 2 year values for the intention-to-treat population with last observation carried forward. *P < 0.001 vs. placebo; †P = 0.002 vs. placebo; ‡P = 0.071 vs. placebo. HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LOCF, last observation carried forward.*

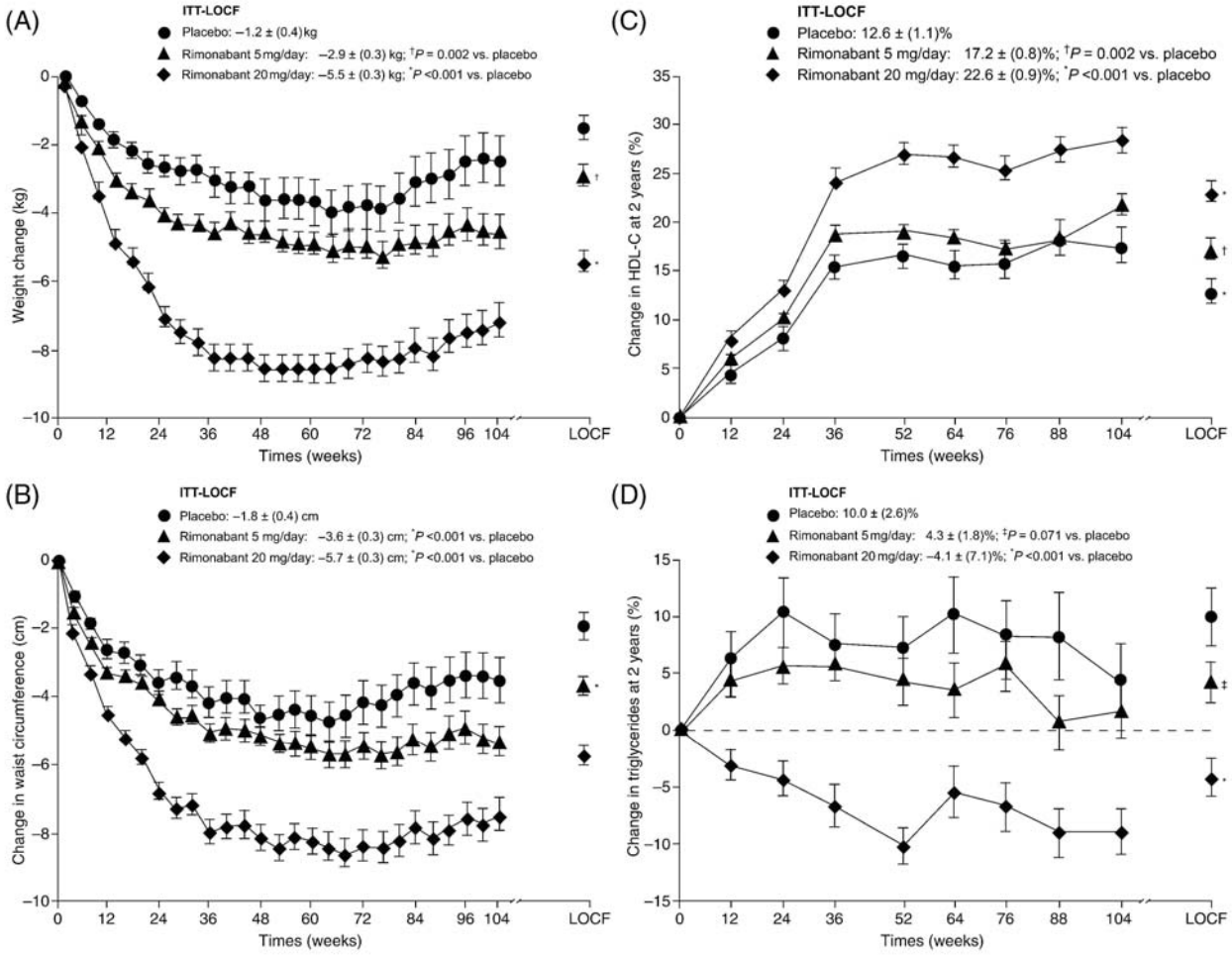

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Table 2: *Changes in cardiometabolic risk factors from baseline to 2 years*[3]

Change from baseline at 2 years	ITT population			Completers		
	Placebo	Rimonabant		Placebo	Rimonabant	
		5mg	20 mg		5mg	20 mg
Weight, kg	-1.2(6.8)	-2.9(6.5), *P* = 0.002	-5.5 (7.7), *P* < 0.001	-2.5 (8.1)	-4.6 (7.6), *P* = 0.007	-7.2 (8.1), *P* < 0.001
Waist, cm	-1.8 (6.8)	-3.6(7.1), *P* < 0.001	-5.7(7.8), *P* < 0.001	-3.4(7.4)	-5.3 (7.9), *P* = 0.023	-7.5 (8.3), *P* < 0.001
HDL-C[b], mmol/L	0.14 (0.23)	0.20 (0.24), *P* = 0.002	0.27 (0.27), *P* < 0.001	0.19(0.25)	0.26 (0.25), *P* = 0.023	0.34 (0.27), *P* < 0.001
TG[b], mmol/L	0.00 (0.71)	-0.06 (0.68), *P* = 0.071	-0.17(0.63), *P* < 0.001	-0.07(0.72)	-0.15 (0.71), *P* = 0.128	-0.23 (0.56), *P* < 0.001
TC[b], mmol/L	0.03 (0.80)	0.05 (0.71), *P* = 0.778	0.09 (0.71), *P* = 0.361	0.01 (0.84)	0.03 (0.69), *P* = 0.844	0.07 (0.71), *P* = 0.575
LDL-C[b], mmol/L	0.16 (0.69)	0.16 (0.65), P = 0.896	0.15 (0.64), *P* = 0.918	0.20 (0.67)	0.19(0.62), *P* = 0.999	0.16 (0.62), *P* = 0.563
TCHDL-C ratio	-0.42 (0.86)	-0.55 (0.81), *P* = 0.024	-0.69(0.77), *P* < 0.001	-0.59 (0.99)	-0.72(0.78), *P* = 0.137	-0.87 (0.73), *P* = 0.002
Non-HDL-C[b], mmol/L	-0.11 (0.77)	-0.15 (0.71), *P* = 0.286	-0.18(0.68), *P* = 0.075	-0.19(0.83)	-0.23 (0.67), *P* = 0.205	-0.27 (0.68), *P* < 0.001
Fasting glucose, mmol/L	0.08 (0.87)	0.01 (0.69), P = 0.166	-0.03 (0.67), *P* = 0.032	0.05 (1.03)	0.06 (0.66), P = 0.932	-0.06 (0.66), *P* = 0.162
OGTT insulin AUC, µlU/mL/min	-80(3162)	-368(3989), *P* = 0.382	-1217(3691), *P* < 0.001	-184(2960)	-663 (3897), *P* = 0.249	-1445 (3848), *P* = 0.003
HOMA-IR	0.8 (4.5)	0.2 (3.5), *P* = 0.040	-0.1 (3.1), *P* = 0.002	0.3 (2.1)	0.1 (4.0), P = 0.499	-0.3 (3.5), *P* = 0.111
SBP, mmHg	0.5 (12.9)	-0.5 (13.2), *P* = 0.263	-0.6(12.7), *P* = 0.199	-0.8(13.8)	-0.7(13.3), *P* = 0.932	-1.8(12.7), *P* = 0.478
DBP, mmHg	-0.3 (8.4)	-0.9(8.7), *P* = 0.309	-1.0(8.8), *P* = 0.242	-1.4(7.6)	-2.1 (9.0), *P* = 0.393	-1.9(8.5), *P* = 0.581

P-values vs. placebo. AUC, area under curve; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model of insulin resistance; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides. [a]Analysis was performed on changes from baseline. Data are presented as mean (SD). [b]Analyses of lipid parameters (except TC:HDL-C ratio) were performed on the per cent change from baseline. Absolute change from baseline was not tested for significance.

Safety and tolerability

The overall 2 year incidence of adverse events was similar in all patient groups *(Table 3)* and lower during the second year of treatment than during the first year. The most common adverse events were infections (nasopharyngitis, influenza), gastrointestinal disorders (nausea), musculoskeletal and connective tissue disorders (back pain, arthralgia), nervous system disorders (headache, dizziness), and psychiatric disorders (anxiety, depressed mood disorders, and disturbances) *(Table 3).* The incidence of psychiatric disorders was higher during year 1 in the rimonabant 20 mg group compared with placebo (23.7 vs. 14.8%), but was almost comparable during year 2 (9.9 vs. 8.3%). Depressed mood disorders and disturbances occurred in 19 patients (6.2%) with placebo, 33 patients (5.5%) with rimonabant 5 mg, and 44 patients (7.3%) with rimonabant 20 mg during year 1, but in only 5 patients (3.0%), 14 patients (3.9%), and 11 patients (3.1%), respectively, during year 2. During the second year of treatment, the rate of withdrawal due to adverse events was lower than in year 1, and similar in all treatment groups *(Table 3).* The most common adverse events leading to study discontinuation were psychiatric disorders, gastrointestinal disorders, and nervous system disorders *(Table 3).* The rate of withdrawal due to psychiatric disorders was low during year 2 (0.6% with placebo, 1.4% with rimonabant 5 mg, and 1.7% with rimonabant 20 mg) *(Table 3).* Totalling all withdrawals due to adverse events over 2 years, the same pattern was seen as for year 1, i.e. a higher withdrawal rate with rimonabant 20 mg than with rimonabant 5 mg or placebo.

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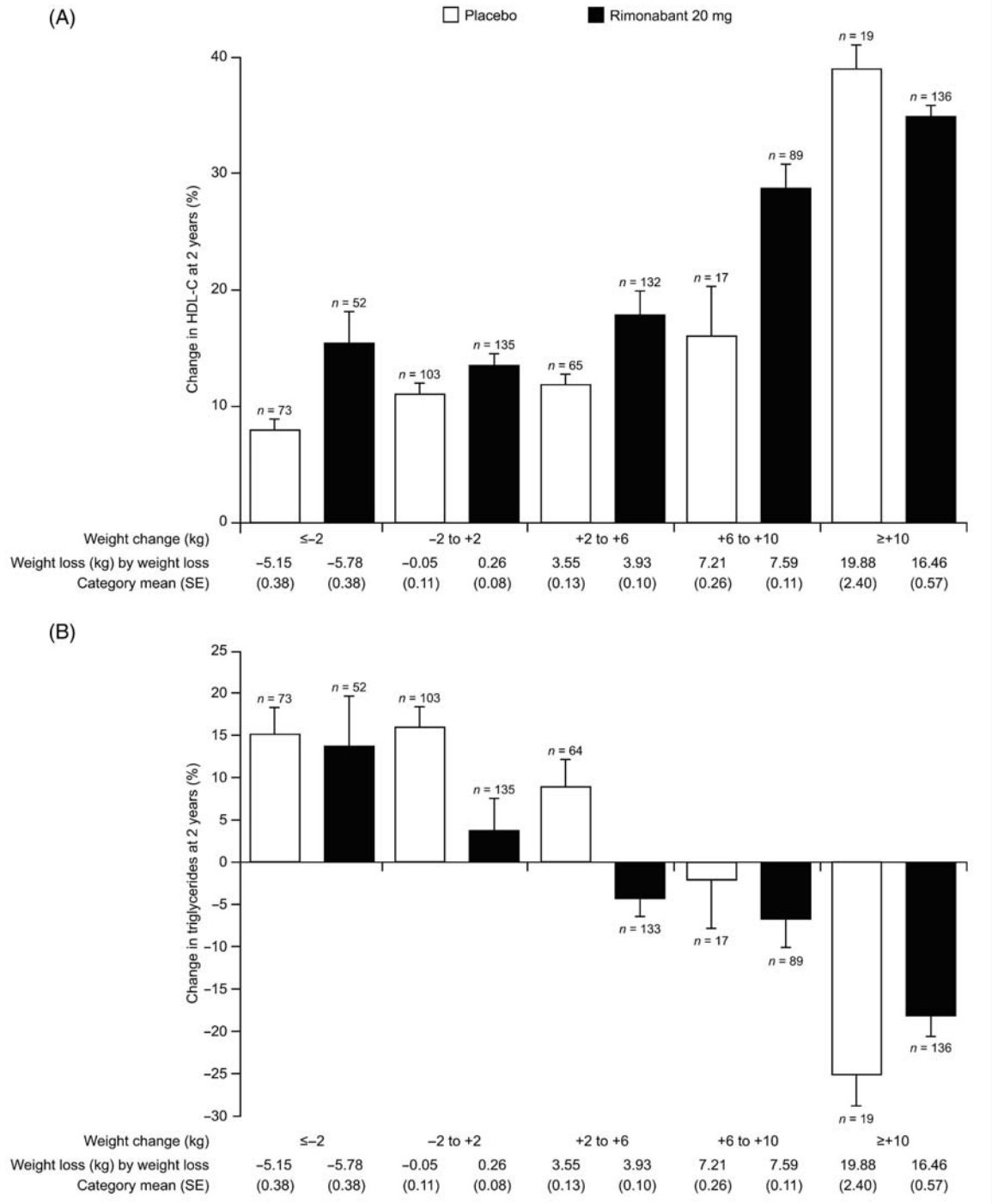
Figure 2: *Relationship between (A) high-density lipoprotein cholesterol and weight loss; (β) triglycerides and weight loss in the intention-to-treat population at 2 years. The selection of the weight loss categories was arbitrary since statistical modelling used to assess the relationships between weight loss and the secondary efficacy endpoints used continuous data. A weight loss of ± 2 kg was chosen as being a reasonable level of no weight loss.*



At 2 years, changes from baseline in the HADS subscores for depression and anxiety were similar to the 1 year results,[16] with no increase from baseline in mean depression subscores over the 2 year period in any treatment group (Supplementary material online, *Table* β). The proportions of patients with clinically significant depression (HADS depression subscore ≥11) at any follow-up visit during the 2 year period were similar in the placebo, rimonabant 5 mg, and rimonabant 20 mg (9.9, 9.9, and 10.2%, respectively); the proportions whose

depression subscore rose by >25% during years 1 and 2 were 50.0, 60.3, and 56.3%, respectively.

At 2 years, there were no clinically significant changes from baseline in heart rate or QTc rate among patients receiving active treatment.

Discussion

Maintenance of weight loss is difficult, and it is common for patients who have lost weight to regain it over a period of several months.[29,30] The primary finding of this study was that the clinically meaningful weight loss, waist reduction, and improvements observed in several cardiometabolic risk factors with rimonabant therapy at 1 year were sustained through the second year of treatment. These results are consistent with the 1 year findings and indicate the durability of the improvements with continuation of double-blind therapy for a second year. These results also corroborate those of the RIO-North America study, where patients who continued to receive rimonabant 20 mg during year 2 maintained their weight loss and accompanying improvements in cardiometabolic risk factors.

As well as weight loss, rimonabant therapy was associated with significant improvements in lipid and glycaemic variables. Whereas the improvements in HDL-C and triglyceride levels were observed concomitantly with a greater reduction in BW during year 1, such improvements in the rimonabant 20 mg group persisted during year 2 when BW was almost stable. Consistent with the 1 year results, the improvement in HDL-C and triglyceride levels exceeded the changes attributable to weight loss alone. This direct peripheral effect of rimonabant on HDL-C and triglyceride levels may be related to enhanced adiponectin mRNA expression in adipose tissue and changes in hepatic enzymes regulating lipid metabolism.[6-8] Unfortunately, adiponectin levels were not measured in the RIO-Europe study. Further studies of the *in vivo* pharmacological effects of rimonabant are needed to advance our understanding of the mechanism of action of rimonabant in peripheral tissues.

Significant improvements from baseline in fasting glucose and fasting insulin were evident after 2 years of treatment with rimonabant 20 mg, which are consistent with the corresponding findings of the RIO-North America study.[18] Furthermore, rimonabant 20 mg was shown to improve glucose tolerance after 2 years in the present study and could help to delay or prevent progression to IGT in overweight and obese patients. Rimonabant 20 mg may also prevent further deterioration of glucose tolerance in patients who already have IGT. Such a hypothesis is currently being evaluated in the RAPSODI trial. Considering the potential role of modest dysglycaemia in the development of cardiovascular disease, the beneficial changes in glucose tolerance after rimonabant treatment are of potential clinical value, especially in combination with the positive effect on lipid profile.

The improvement with rimonabant was statistically significant compared with placebo for the physical function score and the total score, a result which was repeated on the physical functioning domain of the SF-36 questionnaire. Interestingly, this is the only health-related concept measured by both the instruments, and although they address very different levels of physical function, these results clearly indicate a strong positive impact of the drug on physical function in this patient population.

The RIO-Europe 2 year data demonstrated a safety and tolerability profile for rimonabant consistent with that reported during the first year of the study. Rimonabant treatment was generally well tolerated; the most common adverse events experienced by patients on rimonabant 20 mg were mild to moderate in intensity and transient in nature. A recent meta-analysis considering the four RIO clinical trials (1 year data) reported an overall increased risk of depression (OR: 2.51; 95% CI 1.23-5.12), which was, however, lower in RIO-Europe (OR: 1.25; 95% CI 0.55-3.13). It should be noted that 'depression' actually corresponds to 'depressed mood disorders and disturbances'. The present study confirmed these data during the first year, but showed that the incidence of depressed mood disorders and disturbances was low and almost similar between placebo and rimonabant 20 mg during year 2. In addition, although the rate of withdrawals due to psychiatric adverse events was slightly higher with rimonabant than with placebo over the 2 year trial, there were negligible differences between the treatment groups in the HADS depression and anxiety subscores at the end of the study and in the proportion of patients with substantial increases in HADS scores. The data support the long-term (2 year) safety and tolerability of rimonabant in patients included in RIO-Europe, i.e. patients without clinically significant neurological or psychological illness. It should be noted that the revised rimonabant product label excludes patients with antecedents of major depressive illness and/or ongoing antidepressive treatment, because of a higher incidence of psychiatric adverse events in this subgroup.[33]

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Table 3: *Incidence of adverse events*

	Year 1[c]			Year 2 only			Years 1 and 2		
	Placebo (*n* = 305), *n* (%)	Rimonabant		Placebo (*n* = 168), *n* (%)	Rimonabant		Placebo (*n* = 305), *n* (%)	Rimonabant	
		5mg (*n* =603), *n* (%)	20 mg (*n* = 599), *n* (%)		5mg (*n* = 363), *n* (%)	20 mg (*n* = 355), *n* (%)		5mg (*n* = 603), *n* (%)	20 mg (*n* = 599), *n* (%)
Patients with any Adverse event, *n* (%)	253 (83.0)	493 (81.8)	519 (86.6)	124(73.8)	276 (76.0)	280 (78.9)	259 (84.9)	515 (85.4)	534 (89.1)
Serious adverse event, *n* (%)	21 (6.9)	37 (6.1)	49 (8.2)	12(7.1)	13 (3.6)	18 (5.1)	28 (9.2)	50 (8.3)	65 (10.9)
Deaths[a]	1 (0.3)	0(0)	1 (0.2)	1 (0.6)	0(0)	0(0)	2(0.7)	0(0)	1 (0.2)
Adverse event leading to discontinuation, *n* (%)	30 (9.8)	55 (9.1)	95 (15.9)	10(6.0)	11 (3.0)	18 (5.1)	40(13.1)	66 (10.9)	113 (18.9)
Adverse events ≥5% in any treatment group by primary system organ class									
Infections and infestations	146 (47.9)	285 (47.3)	310 (51.8)	80 (47.6)	169 (46.6)	168(47.3)	170 (55.7)	338 (56.1)	355 (59.3)
Psychiatric disorders	45 (14.8)	90 (14.9)	142 (23.7)	14 (8.3)	37 (10.2)	35 (9.9)	54(17.7)	114(18.9)	162(27.0)
Nervous system disorders	69 (22.6)	130(21.6)	150(25.0)	20(11.9)	43 (11.8)	50 (14.1)	81 (26.6)	157 (26.0)	176 (29.4)
Vascular disorders	25 (8.2)	33 (5.5)	50 (8.3)	10(6.0)	16 (4.4)	18 (5.1)	34(11.1)	48 (8.0)	64(10.7)
Gastrointestinal disorders	71 (23.3)	145 (24.0)	190(31.7)	34 (20.2)	63 (17.4)	55 (15.5)	91 (29.8)	180 (29.9)	219 (36.6)
Musculoskeletal and connective tissue disorders	90 (29.5)	182(30.2)	162(27.0)	47 (28.0)	88 (24.2)	100(28.2)	114(37.4)	228 (37.8)	222 (37.1)
General disorders and administration site conditions	37(12.1)	52 (8.6)	57 (9.5)	18(10.7)	28 (7.7)	19 (5.4)	52(17.0)	74(12.3)	71 (11.9)
Adverse event leading to permanent discontinuation by primary system organ class and preferred term									
Infections and infestations	0(0)	2 (0.3)	6 (1.0)	1 (0.6)	0(0)	2 (0.6)	1 (0.3)	2 (0.3)	8 (1.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0(0)	0(0)	3 (0.5)	0(0)	1 (0.3)	2 (0.6)	0(0)	1 (0.2)	5 (0.8)
Metabolism and nutrition disorders	1 (0.3)	4 (0.7)	0(0)	2 (1.2)	1 (0.3)	0(0)	3 (1.0)	5 (0.8)	0(0)
Psychiatric disorders	17(5.6)	18 (3.0)	47 (7.8)	1 (0.6)	5 (1.4)	6(1.7)	18(5.9)	23 (3.8)	53 (8.8)
Depression	4(1.3)	6 (1.0)	14 (2.3)	1 (0.6)	5 (1.4)	3 (0.8)	5 (1.6)	11 (1.8)	17(2.8)
Anxiety	1 (0.3)	0(0)	6 (1.0)	0(0)	0(0)	0(0)	1 (0.3)	0(0)	6 (1.0)
Depressed mood	4(1.3)	4 (0.7)	5 (0.8)	0(0)	0(0)	0(0)	4(1.3)	4 (0.7)	5 (0.8)
Depressive symptom	1 (0.3)	3 (0.5)	4 (0.7)	0(0)	0(0)	0(0)	1 (0.3)	3 (0.5)	4 (0.7)
Major depression	1 (0.3)	0(0)	3 (0.5)	0(0)	0(0)	1 (0.3)	1 (0.3)	0(0)	4 (0.7)
Nervous system disorders	3 (1.0)	9 (1.5)	10(1.7)	1 (0.6)	0(0)	1 (0.3)	4(1.3)	9 (1.5)	11 (1.8)
Headache	0(0)	2 (0.3)	4 (0.7)	0(0)	0(0)	0(0)	0(0)	2 (0.3)	4 (0.7)
Cardiac disorders	4(1.3)	2 (0.3)	5 (0.8)	1 (0.6)	0(0)	1 (0.3)	5 (1.6)	2 (0.3)	6 (1.0)
Vascular disorders	1 (0.3)	1 (0.2)	5 (0.8)	0(0)	0(0)	0(0)	1 (0.3)	1 (0.2)	5 (0.8)
Gastrointestinal disorders	0(0)	5 (0.8)	22 (3.7)	3 (1.8)	1 (0.3)	1 (0.3)	3 (1.0)	6 (1.0)	23 (3.8)
Nausea	0(0)	1 (0.2)	14 (2.3)	0(0)	0(0)	0(0)	0(0)	1 (0.2)	14 (2.3)
Vomiting	0(0)	0(0)	4(0.7)	0(0)	0(0)	0(0)	0(0)	0(0)	4(0.7)
Skin and subcutaneous tissue disorders	1 (0.3)	2 (0.3)	5 (0.8)	0(0)	0(0)	0(0)	1 (0.3)	2 (0.3)	5 (0.8)
General disorders and administration site conditions	1 (0.3)	4 (0.7)	3 (0.5)	0(0)	0(0)	0(0)	1 (0.3)	4 (0.7)	3 (0.5)
Investigations	0(0)	8 (1.3)	3 (0.5)	2(1.2)	1 (0.3)	4(1.1)	2(0.7)	9 (1.5)	7(1.2)

[a]In the placebo group, two patients died: one from a haemorrhage cerebrovascular accident (CVA) and one from multiple haematomas after CVA; in the rimonabant 20 mg group, one patient died due to pulmonary embolism or internal haemorrhage related to advanced adenocarcinoma. No causal relationship to the study drug was suspected by the investigators for any death. In the overall RIO trial programme (n — 6625; four studies), deaths were equally distributed across groups (four in the placebo group, three in the rimonabant 5 mg

group, and four in the rimonabant 20 mg group). According to MedDRA, in at least two patients in any rimonabant groups and in main system organ class (≥1%). One patient may report several events. [c]Adverse events are defined as those occurring during treatment and up to 75 days (five half-lives) after last dose. Year 1 data included only adverse events started during year 1 and not in year 2.

In contrast to the RIO-Lipids and RIO-Diabetes studies, the population of the RIO-Europe study was not selected by the presence of high-risk cardiometabolic factors (overweight/obese patients with or without co-morbidities), and many patients in the current study were at low risk of cardiovascular disease at baseline. Consequently, any change in absolute risk of cardiovascular disease during the study would be difficult to interpret in this patient population and was beyond the scope of the study.

While these 2 year data have demonstrated the durability of the effects of rimonabant on BW, metabolic syndrome, and several lipid and glycaemic variables, the long-term benefits of weight loss and treatment of metabolic syndrome are yet to be substantiated by hard cardiovascular and mortality outcomes. Nevertheless, the substantial increase in HDL-C is one important component that would be expected to confer a reduced risk of cardiovascular disease in these patients. Experience from the Prospective Cardiovascular Munster (PROCAM) study has revealed a significant association between HDL-C and the incidence of atherosclerotic coronary artery disease. However, evidence for the long-term benefit of raising HDL-C levels, as demonstrated by reduced mortality or cardiovascular events, is inconsistent and warrants further investigation. Nevertheless, the continued rise in HDL-C levels with rimonabant 20 mg observed during year 2 is particularly noteworthy because BW was fairly stable during year 2 in this group. Given the increased interest in the role attributed to HDL-C in protection against atherosclerosis, the apparently direct effect of rimonabant 20 mg on HDL-C levels reported here is a worthy candidate for study in future trials.

Conclusions

The 2 year results of RIO-Europe indicate that CB_1 receptor blockade with rimonabant produces durable improvements in several cardiometabolic risk factors. Our data show that most of the benefits observed at year 1 were maintained during year 2, with little evidence of BW regain and no attenuation of the improvements in cardiometabolic risk factors (in contrast, some risk factors showed a trend for further improvements during the second year). Rimonabant 20 mg produced clinically meaningful weight loss and improvements in serum lipid, glucose, and insulin levels, which were maintained over 2 years with favourable safety and tolerability in patients without a history of severe depressive disorder or severe anxiety. Furthermore, rimonabant 20 mg improved HRQoL, particularly physical functioning.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest

L.F.V.G. has received research grants from Fonds Wetenschappelijk Onderzoek, Vlaanderen and from an EU consortium 'Hepadip' project; is on the speaker bureau for Abbott Pharma, AstraZeneca, and sanofi-aventis; is a consultant and member of advisory boards for Abbott Pharma, Amylin Pharma, Johnson & Johnson, Pfizer, and sanofi-aventis. A.J.S. is on the speaker bureau for sanofi-aventis, Pfizer, AstraZeneca, and GlaxoSmithKline; is a consultant and member of advisory boards for sanofi-aventis, GlaxoSmithKline, AstraZeneca, Eli Lilly, Merck-Santé, and Novo Nordisk. A.M.R. is a consultant and member of advisory boards for Abbott Pharma, Eli Lilly, Fournier Pharma, Novo Nordisk, Roche, sanofi-aventis, and Takeda. S.R. is on the speaker bureau for sanofi-aventis, Pfizer, AstraZeneca, GlaxoSmithKline, and Abbott Pharma; is a consultant and member of advisory boards for sanofi-aventis, GlaxoSmithKline, AstraZeneca, Eli Lilly, Novo Nordisk, Roche, Abbott Pharma, and Cederroth Nutrition. C.H. is an employee of sanofi-aventis. O.Z. is on the scientific advisory committee of Eli Lilly, Abbott Pharma, sanofi-aventis, and Roche; has received honoraria from sanofi-aventis, Schering Plough, Merck Sharpe Dohme for GP medical training; has received research support from Servier.

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