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ZIMULTI (rimonabant)
NDA 21-888

Briefing Information for FDA Advisory Committee Meeting

Department: **Regulatory Development**

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LIST OF ABBREVIATIONS

2-AG	2-arachidonoyl-glycerol
ADA	American Diabetes Association
Adj	Adjudication
AE	Adverse event
ACT3801	Craving for food
ACT4855	ACTOL in alcohol dependence
AHA	American Heart Association
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARCI	Addiction Research Center Inventory
ARIC	Atherosclerosis Risk In Communities
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
C-CASA	Columbia-Classification of Adult Suicidality Assessment
CB_1 or CB_2	Central cannabinoid receptor type 1 or 2
CI	Confidence interval
C_{max}	Maximum plasma concentration observed in the dosing interval, during repeated dosing
CNS	Central nervous system
CYP	Cytochrome P450
DGT	Diabetic glucose tolerance
DIO	Diet induced obesity
DRI	Dose ranging study
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
ECS	Endocannabinoid system
ECG	Electrocardiogram
EEG	Electroencephalogram
EFC4474	STRATUS-EU
EFC4733	RIO-Europe
EFC4735	RIO-Lipids
EFC4736	RIO-Diabetes
EFC4743	RIO-North America
EFC4796	STRATUS-WW
EFC4798	CIRRUS
EFC4964	STRATUS-US
EFC5031	REBA
EFC5107	RAPSODI
EFC5593	APPEGGIO
EFC5745	INSULIN CLAMP
EFC5794	STRATUS-META

EFC5823	ADAGIO-Lipids
EFC5825	SERENADE
EFC5826	CRESCENDO
EFC5827	STRADIVARIUS
EFC5828	AUDITOR
EFC6001	RIO-ASIA
EMEA	European Medicines Agency
FAAH	Fatty acid amide hydrolase
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HAD	Hospital Anxiety and Depression
HbA_{1c}	Glycosylated hemoglobin (hemoglobin A_{1c})
HDL-C	High-density lipoprotein cholesterol
HLGT	High level group term
HLT	High level term
HOMA	Homeostasis model assessment of insulin resistance
HR	Heart rate
ICH	International Conference on Harmonisation
IFG	Impaired fasting glucose
INT	Drug interaction study
IOTF	International Obesity Task Force
IP	Intraperitoneal
ITT	Intent to Treat
LDL-C	Low-density lipoprotein cholesterol
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NEC	Not elsewhere classified
NOS	Not otherwise specified
OGTT	Oral glucose tolerance test
PDY	Pharmacodynamics study
pgp	p-glycoprotein
PKD	Pharmacokinetic-pharmacodynamic correlation study
PMC0172	VICTORIA
POP	Population study
PSUR	Periodic safety update report
PT	Preferred term
PTZ	pentylenetetrazole
QD	Once a day
QRS	Distance in time on the ECG tracing from the start of the Q-wave to the end of the S-wave
QT	Distance in time on the ECG tracing from the start of the QRS-complex to the end of the T-wave
QTc	QT interval corrected

RIO	Rimonabant in obesity
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
STRATUS	Studies with rimonabant and tobacco use
TDR	Tolerance after repeated dose administration study
TDU	Tolerance after single ascending dose administration study
TEAEs	Treatment-emergent adverse event(s)
TG	Triglycerides
THIN	The Health Information Network
TID	Three times a day
t_{max}	Temperature maximum
TNFα	Tumor necrosis factor α
US	United States
WHO-ART	World Health Organization Adverse Reaction Terminology

1. EXECUTIVE SUMMARY

1.1 Background

This briefing package is being provided to the Endocrinologic and Metabolic Drugs Advisory Committee of the United States (US) Food and Drug Administration (FDA) for the public meeting scheduled on 13 June 2007. During this meeting, the committee will discuss the safety and efficacy of sanofi-aventis' new drug application (NDA) 21-888, ZIMULTI® (rimonabant), 20 mg.

Sanofi-aventis completed a global development program with rimonabant and submitted a NDA to the FDA in April 2005. Following the filing of the NDA, the FDA administratively divided the application to facilitate the review of the obesity/diabetes indications within the Division of Metabolism and Endocrinology Products and the indication for smoking cessation within the Division of Anesthetic, Analgesia, and Rheumatology Products. Following the review of the NDA, the FDA issued an Approvable letter to sanofi-aventis in February 2006 to support the efficacy of rimonabant 20-mg for obesity and a Not Approvable action letter for the indication of smoking cessation due to lack of efficacy.

Representatives from sanofi-aventis and the FDA met to review the action letters and discussed the actions needed to facilitate review of the NDA for obesity with cardiovascular risks. Sanofi-aventis submitted a complete response to the Approvable Action Letter in October 2006, this submission provided revised labeling with the following proposed indications:

- ZIMULTI® is indicated as an adjunct to diet and exercise for the treatment of overweight patients with body mass index (BMI) >27 kg/m^2 and at least 1 other cardiovascular risk factor, or for the treatment of obese patients with a BMI ≥30 kg/m^2;
- ZIMULTI® is also indicated in combination with metformin or a sulfonylurea to improve glycemic control and reduce weight in patients with type 2 diabetes and a BMI >27 kg/m^2 when diet and exercise plus a single agent do not result in adequate control.

During the advisory committee meeting, sanofi-aventis will focus on the safety and efficacy characteristics of rimonabant, the medical need and benefit-risk of the drug in obese patients and patients with type 2 diabetes, and the proposed risk management plan for ZIMULTI®.

1.2 Development plan/global regulatory status

Obesity is a chronic and highly prevalent illness frequently associated with numerous and sometimes fatal diseases. Contrary to just being a medical condition or risk factor for other diseases, obesity is a complex disease of multifaceted etiology (including environmental factors and genetic predisposition), with its own disabling capacities, pathophysiology, and comorbidities. Some of the comorbidities of obesity include type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, and cardiovascular disease. Despite the severity of this condition, there are very few anti-obesity agents approved for marketing and none targeting the complex metabolic disorders of this disease. An effective treatment of the causes of the metabolic complications of obesity is still needed, and current guidelines for the treatment of obesity support pharmacotherapy as an adjunct to diet and exercise.

There have been increasing numbers of government initiatives from the Food and Drug Administration (FDA), the National Institute of Health (NIH), and others to address the epidemic of obesity and associated comorbidities including hypertension, type 2 diabetes, and dyslipidemia. In 1996, the FDA published the draft guidance for the Clinical Evaluation of Weight-Control Drugs. This guidance outlined the criteria for regulatory approval for drugs to treat obesity, which included a minimum of one year of placebo-controlled exposure in 1500 patients and a second year of exposure in up to 500 patients. The efficacy criteria established by the guidance stipulated that the mean weight loss be 5% greater in drug versus placebo-treated patients or, that the proportion of patients losing 5% of their weight be greater in the drug versus placebo-treated group. Additionally, the populations to be studied in these trials were recommended to be patients with a body mass index (BMI) greater than 30 or greater than or equal to 27 with comorbidities such as hypertension, type 2 diabetes, and dyslipidemia. The pivotal clinical studies with rimonabant performed by sanofi-aventis met these criteria established by the FDA guidance document.

In 1998-2000, the NIH established clinical guidelines for the treatment of overweight and obesity. In addition to establishing a BMI classification based on epidemiology data that showed increases in mortality with BMIs greater than 25, the guidelines also stated that “weight loss medications should be used only by patients who are at increased medical risk because of their weight and should not be used for cosmetic weight loss.” Furthermore, weight loss medications should never be used without concomitant lifestyle modifications. Importantly, the guidelines also recognized that obesity is a chronic disorder (disease) and that short-term treatment with anti-obesity pharmacotherapy is not helpful. Rimonabant has been developed for those patients at increased medical risk due to their overweight or obesity. Rimonabant, in combination with lifestyle modifications, provides a medical therapy for a chronic disease.

In September 2004, the Endocrinologic and Metabolic Drugs Advisory Committee met to consider revisions to the draft 1996 FDA guideline. The committee agreed that the size of trials for the development of obesity drugs should be driven by the safety of the drug and that one-year placebo-controlled exposure in these trials should be supported. The efficacy criteria established by the 1996 FDA guideline that the mean weight loss be 5% greater in drug versus placebo-treated patients or, that the proportion of patients losing 5% of their weight be greater in the drug versus placebo-treated group was also supported by the committee. Importantly, the committee strongly recommended the continued evaluation of safety and efficacy in patient populations with BMIs greater than 30 or greater than or equal to 27 with comorbidities.

Earlier this year, the FDA published for public review and comment, a revised draft guideline entitled: Developing Products for Weight Management. The rimonabant development program has met the safety and efficacy criteria outlined in the guidance document.

ZIMULTI® (rimonabant) is a new molecular entity and is the first cannabinoid type 1 (CB_1) receptor antagonist to be developed for indications in obesity and for the treatment of patients with type 2 diabetes mellitus. The recommended therapeutic dose of rimonabant 20-mg was determined following the completion of a Phase 2 dose-ranging study in obese subjects. A total of 12 836 patients were exposed to rimonabant in Phase 3 studies (7447 to rimonabant 20-mg; 3478 patient-years), 1008 patients were exposed in 6 Phase 2 studies and 1190 healthy subjects were exposed to rimonabant in 40 Phase 1 studies [Table (1.7) 1]. The presentation in this briefing package of the safety and efficacy data from these studies is focused on supporting the proposed indications in obesity and patients with type 2 diabetes mellitus. Where appropriate (SAEs, seizures, and suicidality-related events), other populations will be considered.

In addition to the completed studies, there were 11 ongoing blinded clinical studies as of 01 March 2007, including 3 Phase 1 studies and 8 pivotal clinical trials, involving an additional 14 280 patients, that had randomization ratios of 1:1 (rimonabant: placebo). These studies are evaluating the safety and efficacy of rimonabant in obese patients with comorbidities including type 2 diabetes mellitus, dyslipidemia, and cardiovascular risk factors. Included in these trials are a cardiovascular outcomes study, CRESCENDO, and 2 morphometric imaging studies. Analysis of rare safety events of interest is also presented for these ongoing studies.

1.3 Mechanism of action

CB_1 receptors are part of the endocannabinoid system or ECS. The ECS role encompasses regulation, coordination, and integration of the central behavioral aspects of nutrient intake with the peripheral modulation of nutrient transport, metabolism, and storage in gut, liver, adipose tissue, muscle, and the pancreas. The over activity of the ECS translates into centrally mediated increases in energy intake, while favoring peripheral energy storage, to the detriment of its metabolic use. Moreover, ECS dysregulation is implicated in the underlying etiology of obesity and related metabolic disorders.

Rimonabant is the first potent and selective antagonist of CB_1 receptors. As such rimonabant affects CB_1 receptor blockade that contributes to: 1) the normalization of metabolic functions via central effects on energy intake leading to a decrease of body weight; and 2) peripheral effects in muscle, liver, and adipose tissue favoring insulin sensitivity and glucose homeostasis. These effects in turn translate into beneficial modulation of glycemia, glycosylated hemoglobin (hemoglobin A_{1c}) (HbA_{1c}), and triglyceride (TG) flux [TG and high-density lipoprotein cholesterol (HDL-C) levels], above and beyond the body weight decrease, as reported in clinical studies with rimonabant in obese/overweight patients.

1.4 Nonclinical studies

In a comprehensive program of nonclinical studies, rimonabant was shown to have very limited potential to induce toxicity. No specific target organ pathology was identified in the completed animal studies. The nonclinical studies suggest a weak, proconvulsant potential for rimonabant when combined with pentylenetetrazole that alone induces convulsions under experimental procedures in some species. These data are consistent with the view that rimonabant is without proconvulsant potential in the absence of other stressors. Results from the literature and from in-house studies showed that rimonabant had no effect on neuronal excitability in animals when administered alone. Based on the animal findings, seizures were carefully monitored during controlled clinical studies.

1.5 Clinical pharmacology

The pharmacokinetic profile of rimonabant was characterized by a rapid absorption; a large distribution with high plasma protein binding, metabolism, and elimination mainly by the liver; and a long terminal half-life. The terminal half-life of rimonabant is 6 to 9 days in healthy (normal weight) subjects and the time to reach steady state after a once-daily dose is 13 days, with a 3.3-fold accumulation. Higher body weight results in a higher peripheral volume of distribution of rimonabant, which leads to a longer terminal half-life (16 days) and time to reach steady state (25 days) observed in obese subjects. Since clearance after oral administration is not affected by body weight, there are fewer fluctuations in peak-to-trough plasma concentrations, but no difference in total plasma exposure (AUC_{0-24}) in obese subjects compared with normal weight subjects was observed.

The global pharmacokinetic profile justifies a once-daily dose regimen without dose adjustment in age, gender, or body weight. Black patients appeared to be less exposed to rimonabant than Caucasians. An interaction study with ketoconazole, a potent cytochrome P450 (CYP) 3A inhibitor, caused an approximate 2-fold increase in rimonabant exposure; therefore, significant drug-drug interactions due to CYP3A inhibition are unlikely. This observation was further supported by the lack of signal detected in the analysis of the extensive clinical database of rimonabant in smokers and obese patients. Rimonabant dose modifications are not recommended in coadministration with substrates, inhibitors, or inducers of other CYP isozymes or substrates of P-gp, or based on smoking status or hepatic (mild and moderate) or renal impairment.

Studies were performed in healthy volunteers with rimonabant up to 300 mg as a single dose and up to 80 mg as repeated doses. In addition, an electrocardiogram (ECG) study of 4 weeks duration was performed with the proposed therapeutic dose of rimonabant 20-mg and a supratherapeutic dose of 60 mg (maximum tolerated dose) up to 28 days in duration. This study was conducted in accordance to the International Conference on Harmonisation (ICH) guidance. In this study, rimonabant did not prolong cardiac repolarization at either the therapeutic or supratherapeutic dose.

1.6 Clinical efficacy

1.6.1 Obesity

The 2 doses used in the Phase 3 clinical development program of rimonabant for the treatment of obesity were selected from the dose-ranging study conducted in 287 patients (BMI $\geq$27 kg/m^2 with 3 doses of rimonabant (5-, 10-, and 20-mg, once daily) and a placebo. Compared with the placebo, rimonabant significantly reduced body weight in a dose-related manner in obese patients over a 4-month period of treatment [difference versus placebo: for 5-mg -1.6 kg (-3.5 lbs) (p=0.009), for 10-mg -1.8 kg (-4.0 lbs) (p=0.03), and for 20-mg -2.9 kg (-6.4 lbs) (p=0.0001)]. Additionally, a study conducted at 40-mg for 1 month in 44 patients showed a significant body weight loss (-2.9 kg) (-6.4 lbs) but the rate of nausea was 39.1%. Based on theses results, the Phase 3 studies evaluated 20-mg and 5-mg doses versus placebo.

The efficacy of rimonabant in the treatment of obesity has been demonstrated in 4 adequate and well-controlled studies (the RIO studies), for up to 1 year and for 2 years in 2 of the studies.

Rimonabant 20-mg used in conjunction with a modest calorie diet and physical exercise significantly decreases body weight and waist circumference in overweight or obese patients [Table (1.6.1) 1].

Table (1.6.1) 1 - Mean weight change (lbs) from baseline in obese and overweight patients treated with rimonabant 5-mg and rimonabant 20-mg versus placebo at 1 year (ITT analysis)

Study	Placebo	Rimonabant 5 mg	Rimonabant 20 mg
RIO-North America	N=590 -3.4	N=1191 -6.4	N=1189 -13.8
RIO-Europe	N=302 -4.0	N=597 -7.4	N=595 -14.5
RIO-Lipids	N=334 -3.3	N=340 -6.8	N=344 -15.3
RIO-Diabetes	N=345 -3.2	N=355 -5.1	N=336 -11.7

p<0.001 for the difference versus placebo in all comparisons
ITT: Intent-to-treat; RIO: Rimonabant in obesity

Specific details regarding the designs of the 4 Phase 3 studies are presented in Figure (6.1) 1.

In addition, in all 4 studies, rimonabant improved several metabolic parameters associated with obesity, including HDL-C, TG [Table (1.6.1) 2], and insulin, above and beyond the effect of body weight loss.

Table (1.6.1) 2 - HDL-C and TG (mmol/L) at 1 year (*) - RIO studies

	RIO-North America		**RIO-Europe**		**RIO-Lipids**		**RIO-Diabetes**	
	Placebo (N=607)	**20 mg (N=1219)**	**Placebo (N=305)**	**20 mg (N=599)**	**Placebo (N=342)**	**20 mg (N=346)**	**Placebo (N=348)**	**20 mg (N=339)**
% Change - HDL-cholesterol (HDL-C)								
Mean	5.4	12.6	13.4	22.3	11.0	19.1	7.1	15.4
LS Mean		7.2		8.9		8.1		8.4
% Change -Triglycerides (TG)								
Mean	7.9	-5.3	8.3	-6.8	-0.2	-12.6	7.3	-9.1
LS Mean		-13.2		-15.1		-12.4		-16.4

p<0.001 for the difference versus placebo in all comparisons
(*) Intent-To-Treat (ITT) analysis
LS Mean: least squares mean

In the 3 studies that included nondiabetic patients, the proportion of patients who lost at least 5% of baseline body weight was 50.8% in the rimonabant 20-mg group and 19.7% in patients in the placebo group (p<0.001). Twenty-seven percent of patients in the rimonabant 20-mg group lost at least 10.0% of baseline body weight (7.8% in placebo, p<0.001). The efficacy criteria established by the FDA guidance document stipulated that the mean weight loss be 5% greater in drug versus placebo treated patients or, that the proportion of patients losing 5% of their weight be greater in the drug versus placebo-treated groups.

In severely obese patients (BMI ≥40 kg/m^2), rimonabant 20-mg decreased body weight and improved metabolic parameters. Rimonabant 20-mg almost halved the percentage of patients with severe obesity after 1 year of treatment. One patient out of 4 lost more than 10% of their baseline body weight, tripling the effect of the diet alone (placebo).

As expected for this chronic disease, when treatment is discontinued after 1 year, body weight regain occurred. In contrast, the body weight loss and metabolic improvements are maintained when rimonabant was continued for up to 2 years as demonstrated in 2 studies [Figure (6.1) 3].

The 5-mg dose had an effect of limited clinical interest on metabolic parameters in spite of a clinically significant effect on body weight compared to placebo.

1.6.2 Type 2 Diabetes

Two studies were conducted in type 2 diabetic patients:

- ***RIO-Diabetes*** was conducted in patients who did not achieve adequate glycemic control on a diet plus a single oral antidiabetic agent (metformin or sulfonylureas). Rimonabant at the dose of 20-mg once daily significantly decreased HbA_{1c}, body weight and TG, and significantly increased HDL-C [Figure (1.6.2) 1]. The effects were demonstrated equally in patients taking metformin or a sulfonylurea. Approximately half of these effects on glucose control and lipids are independent of body weight loss (Section 6.4).

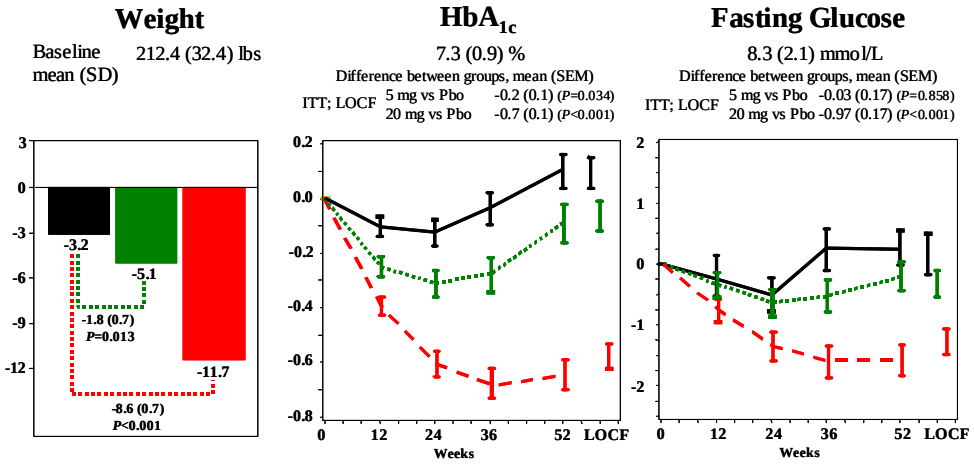

Figure (1.6.2) 1 - RIO-Diabetes study results

- ***SERENADE*** was a study comparing rimonabant 20-mg and placebo in oral antidiabetic drug-naive patients. Rimonabant significantly decreased HbA_{1c} and body weight [Figure (1.6.2) 2], and also decreased TG over placebo and increased HDL-C over placebo.

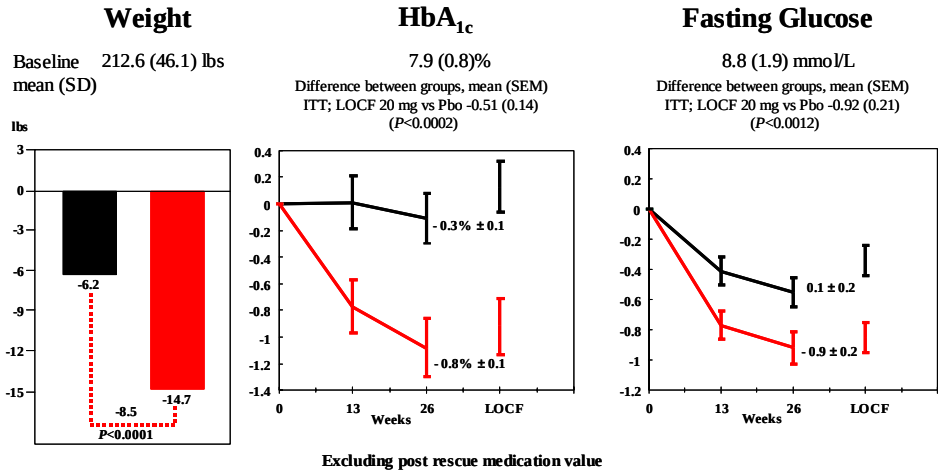

Figure (1.6.2) 2 - SERENADE study results

In the treatment of obesity, the efficacy of rimonabant 20-mg used in conjunction with a reduced calorie diet and physical exercise was demonstrated in 4 adequate and well-controlled studies with reproducible results, and sustained over time, up to 1 year in all 4 studies, and up to 2 years in 2 studies. Rimonabant 20-mg also demonstrated favorable metabolic effects including increased HDL-C and decreased TG, above and beyond its significant effect on body weight loss. In the treatment of diabetes, 2 studies demonstrated that rimonabant 20-mg significantly improved glucose control and decreased body weight, with the same improvements in dyslipidemia associated with type 2 diabetes as in nondiabetic patients.

1.7 Clinical safety

Overall rimonabant clinical program

The rimonabant clinical program included 59 clinical studies completed as of 01 March 2007, involving over 16 000 subjects or patients, of whom 15 034 were exposed to at least 1 dose of rimonabant, as follows:

- 1190 healthy subjects were enrolled in 40 Phase 1 studies during which they received single (1 mg up to 300 mg) or multiple (1 mg up to 80 mg daily for 6 days up to 4 weeks) doses of rimonabant;
- 1008 patients were enrolled in 6 Phase 2 studies conducted in various indications (obesity, smoking cessation, alcoholism, and schizophrenia), where they received multiple doses of rimonabant 5, 10, 20, or 40 mg daily from 6 weeks up to 24 weeks;
- 12 836 patients were enrolled in 13 Phase 3 studies conducted in 3 different programs [Table (1.7) 1] where they received 5-mg or 20-mg for up to 2 years.

Table (1.7) 1 - Number of patients exposed to any treatment in completed Phase 3 studies

Study Name	Placebo	Rimonabant		
		5 mg	20 mg	All doses
Obese patients				
RIO-Europe	305	603	599	1202
RIO-North America	1233	1214	1219	2433
RIO-Lipids	342	345	346	691
RIO-Diabetes*	348	358	339	697
Binge Eaters	146	-	143	143
REBA (Eating behavior)	80	-	76	76
EFC5745	20	-	20	20
Sub-total obesity	2474	2520	2742	5262
Sub total pt-year	2177	2421	2529	
Smokers patients				
STRATUS-US	261	262	261	523
STRATUS-EU	260	256	267	523
STRATUS-META	268		262	262
STRATUS-WW		2351	3023	5374
CIRRUS	-	-	754	754
Sub-total smoking cessation	1453	2869	4567	7436
Sub total pt-year	494	766	889	
TOTAL obesity and smoking cessation	3927	5389	7309	
Total pt-year	2671	3187	3419	
Type 2 diabetes patients				
*RIO-Diabetes**	*348*	*358*	*339*	*697*
SERENADE	140	-	138	138
Sub-total	488	358	477	835
Sub total pt-year	341	283	328	
TOTAL obesity, type 2 diabetes and smoking cessation	4067	5389	7447	12836
Total pt-year	2734	3187	3478	

* Patients from RIO-diabetes study are presented both in obesity and type 2 diabetes and are counted in the totals.

In addition to this large development program, with 3 478 patient-years exposed to rimonabant 20-mg, there were 11 ongoing studies as of 01 March 2007 (3 Phase 1 studies and 8 Phase 3 studies) involving a large population (14 280 patients, blinded treatment, 1:1 randomization ratio of placebo to rimonabant 20-mg, representing 7855 patient-years of which half [3927] apply to rimonabant 20-mg).

Overall safety profile

The primary focus of this briefing document is to present the data from the obesity and diabetes programs. Global pooling is presented for rare events, and the smoking cessation program is discussed where the profile of safety is different from that observed in the obesity program.

Extensive clinical safety data were collected from this clinical development program and allowed a comprehensive review of the safety profile of rimonabant. In the Phase 1 or Phase 2 studies, the adverse events (AEs) more frequently reported with rimonabant than in placebo treated-individuals were gastrointestinal (GI) (nausea, vomiting), nervous system (dizziness, paresthesia, tremor), psychiatric (anxiety, insomnia), and general (asthenia/fatigue, disturbance in attention) disorders. In the Phase 3 obesity program, the most commonly reported AEs with rimonabant when compared with placebo were consistent with those observed in the Phase 1 and Phase 2 studies [Table (1.7) 2]. In the diabetic population, the events were of the same nature when compared to the obese population as a whole, with the exception of some specific events, possibly condition-related events (eg, hypoglycemia) [Table (7.4.1.2.1) 2].

Table (1.7) 2 - Obesity program - AEs reported in ≥2% in the rimonabant 20-mg group and ≥1% over placebo

SOC PT	**Placebo (N=2474) %**	**Rimonabant 5 mg (N=2520) %**	**Rimonabant 20 mg (N=2742) %**
Gastrointestinal disorders			
Nausea	4.7	6.9	13.6
Diarrhea	5.8	7.5	7.7
Vomiting	2.3	3.0	4.7
Nervous system disorders			
Dizziness	4.1	5.9	7.3
Psychiatric disorders			
Anxiety	2.1	2.9	5.9
Insomnia	3.4	3.2	5.8
Mood alterations with depressive symptoms	2.8	3.6	4.7
Depressive disorders	1.7	2.8	3.9
Miscellaneous			
Influenza	9.1	9.2	10.3
Asthenia/fatigue	4.4	5.0	6.1
Contusion	1.1	1.9	3.1
Hot flush	0.8	1.3	2.0

N= patients exposed to treatment at any time.

The incidence of SAEs displayed by SOC reported in ≥0.5% of patients in the rimonabant 20-mg group and reported more often than placebo is presented in Table (1.7) 3. In the Phase 3 obesity program, the rates of serious AEs (SAEs) were similar across treatment groups [Table (1.7) 3]. Consistent rates were observed in the diabetic population. When considering the global pooling of the obesity and smoking cessation studies, the rates of SAEs were 3.6% in the rimonabant 20-mg group, 3.8% in the rimonabant 5-mg group, and 3.9% in the placebo group.

Table (1.7) 3 - Obesity program - incidence of SAEs displayed by SOC reported in ≥0.5% of the rimonabant 20-mg group and reported more often than placebo

n (%)	**Placebo (N=2474)**		**Rimonabant 5 mg (N=2520)**		**Rimonabant 20 mg (N=2742)**	
Any SAEs	*106*	*(4.3)*	*153*	*(6.1)*	*175*	*(6.4)*
Including Fatal SAEs	*3*	*(0.12)*	*3*	*(0.12)*	*4*	*(0.15)*
Neoplasms benign, malignant	15	(0.6)	22	(0.9)	27	(1.0)
Infections & Infestations	13	(0.5)	15	(0.6)	21	(0.8)
Injury & procedural complications	8	(0.3)	17	(0.7)	20	(0.7)
Gastrointestinal disorders	13	(0.5)	14	(0.6)	18	(0.7)
Psychiatric disorders	2	(<0.1)	6	(0.2)	15	(0.5)

N= patients exposed to treatment at any time
SOC = system organ class

Overall, 18 fatal outcomes were reported in the rimonabant clinical program completed as of 01 March 2007; 4 cases were off drug and 14 cases occurred during the study treatment period. Of the 14 cases that occurred during study treatment, 10 were observed in the obesity studies with similar rates across treatment groups (0.15% in the rimonabant 20-mg group, 0.12% in the rimonabant 5-mg group, and 0.12% in the placebo group) [Table (1.7) 4]. Concerning the 4 other cases, 1 case of subdural hemorrhage was observed in the SERENADE study in the placebo group, and the 3 others occurred during the smoking cessation studies (2 in the rimonabant 20-mg group: coronary artery sclerosis and road traffic accident, and 1 cardio-respiratory arrest in the placebo group). Thus, deaths were equally distributed across treatment groups and did not show any specific pattern.

Table (1.7) 4 - Obesity program - fatal SAEs

Reason for death	**Placebo (N=2474)**	**Rimonabant 5 mg (N=2520)**	**Rimonabant 20 mg (N=2742)**
Fatal SAEs	*3 (0.12)*	*3 (0.12)*	*4 (0.15)*
Cardiac arrest	-	1	-
Cardiac failure	-	-	1
Coronary artery disease	-	-	1
Cerebral hematoma/CVA	1	-	-
Cerebral hemorrhage	1	-	-
Pulmonary embolism	1	-	-
Septic shock	-	1	-
Completed suicide	-	1	-
Road traffic accident (as passenger)	-	-	1
Uterine cancer (end-stage)	-	-	1

N= patients exposed to treatment at any time.

In the Phase 3 program, the primary reasons for discontinuing rimonabant reflected the common safety profile of the drug and the requirement to discontinue for antidepressant treatment since the use of antidepressants often cause weight gain [Table (1.7) 5].

Table (1.7) 5 - Obesity program - discontinuation due to AEs reported in ≥0.5% in the rimonabant 20-mg group

	Placebo (N=2474) %	**Rimonabant 5 mg (N=2520) %**	**Rimonabant 20 mg (N=2742) %**
Patient discontinuations due to AEs	*7.6*	*11.0*	*15.5*
Depressive disorders	1.0	1.5	2.3
Nausea	<0.1	0.2	1.5
Anxiety	0.2	0.3	1.2
Mood alterations with depressive symptoms	0.7	1.0	1.2
Dizziness	0.1	0.2	0.7
Pregnancy*	0.4	1.3	0.7
Headache	0.3	0.4	0.5
Insomnia	0.2	0.1	0.4

N= patients exposed to treatment at any time. * pre-specified withdrawal criterion as per protocols

Two categories of AEs of interest have been identified and are being closely monitored. These are psychiatric events (anxiety and depressive events, including suicidality) and neurological events (sensory changes, motor impairment, and cognitive difficulties) including seizures.

Psychiatric events

Anxiety disorders and symptoms included various manifestations of anxiety (such as anxiety, nervousness, panic attack, or panic reaction), with higher incidences in the rimonabant groups when compared with placebo [Table (1.7) 6]. Most of these cases were mild and transient.

These events were nonserious in a large majority of cases, but 2 cases were serious under rimonabant. Corrective treatment was reported (mostly anxiolytics in 48% and 41%of cases for placebo and, rimonabant respectively). Eighty percent of patients experiencing these events continued rimonabant treatment.

Table (1.7) 6 - Obesity programs - anxiety disorders and symptoms

	Obesity studies					
ANXIETY DISORDERS AND SYMPTOMS	**Placebo (N=2474) n (%)**		**5 mg (N=2520) n (%)**		**20 mg (N=2742) n (%)**	
Anxiety disorders & symptoms	*100*	*(4.0)*	*141*	*(5.6)*	*278*	*(10.1)*
Anxiety symptoms	95	(3.8)	130	(5.2)	246	(9.0)
Panic disorders	1	(<0.1)	4	(0.1)	23	(0.8)
Specific and social phobic disorders	2	(<0.1)	0	(0.0)	5	(0.2)
Stress disorders	2	(<0.1)	7	(0.3)	6	(0.2)
Anxiety disorders nec	1	(<0.1)	1	(<0.1)	3	(0.1)
Fear symptoms	0	(0.0)	0	(0.0)	1	(<0.1)

N= patients exposed to any treatment throughout entire study

Depressive events were more frequent under rimonabant [Table (1.7) 7]. In the clinical Phase 3 program, patients with a past history of severe depression or patients with current severe psychiatric illness were excluded. Antidepressant treatment was not permitted and warranted mandatory treatment discontinuation, as prespecified by the protocols.

Table (1.7) 7 - Number (%) of patients with depressed mood disorders and disturbances (≥0.1%) in obesity

	Placebo (N=2474) n (%)	**5 mg (N=2520) n (%)**	**20 mg (N=2742) n(%)**
Depressed mood disorders and disturbances	112 (4.5)	158 (6.3)	231 (8.4)
Depressive disorders	43 (1.7)	70 (2.8)	106 (3.9)
Depression	34 (1.4)	56 (2.2)	87 (3.2)
Dysthymic disorder	0 (0)	7 (0.3)	4 (0.1)
Major depression	9 (0.4)	7 (0.3)	15 (0.5)
Mood alterations with depressive symptoms	70 (2.8)	91 (3.6)	129 (4.7)
Anhedonia	1 (<0.1)	0 (0)	3 (0.1)
Decreased interest	1 (<0.1)	0 (0)	0 (0)
Depressed mood	57 (2.3)	76 (3.0)	96 (3.5)
Depressive symptom	14 (0.6)	15 (0.6)	29 (1.1)
Feeling of despair	0 (0)	1 (<0.1)	0 (0)
Tearfulness	0 (0)	0 (0)	4 (0.1)

N= patients exposed to any treatment throughout entire study

Two different categories of events were reported: depressive disorders and mood alterations with depressive symptoms. In the obesity program, depressive disorders (depression, major depression, and dysthymic disorders) were reported more frequently in the rimonabant 20-mg group (3.9%) when compared with the placebo group (1.7%). Around 70% of patients required corrective treatment (placebo: 31/43; rimonabant 5-mg: 48/70; rimonabant 20-mg: 76/106) and the rate of discontinuation due to depressive disorders was around 60% (placebo: 25/43; rimonabant 5-mg: 39/70; rimonabant 20-mg: 64/106). Four patients under rimonabant 20-mg were hospitalized. These events occurred early in the course of the treatment, with one-half of the events starting within 3 months after rimonabant was given. Past history of depressive disorders is the main risk factor that has been identified (8-fold, regardless of the group) for depressive disorders.

Mood alterations were reported more frequently in the rimonabant 20-mg group when compared with the placebo group in obese patients (rimonabant 20-mg: 4.7%, placebo: 2.8%). Contrary to what was observed for depressive disorders, most of the patients with mood alteration events were not treated (corrective therapy 28.7% for rimonabant compared to 34.8% for placebo), and the study treatment was continued for 75% of the patients with this type of event, whatever the group of treatment. No mood alteration event led to hospitalization.

Although the literature is unclear with respect to the relationship between weight loss and depression, increased rates of psychiatric events, including depression, have been reported with weight loss agents in their package inserts: orlistat (Xenical) (depression: 3.4% versus 2.5% at Year 2) and sibutramine (Meridia) (depression: 4.3% versus 2.5%, and emotional liability: 1.3% versus 0.6%) for active drug versus placebo, respectively.

In the completed studies, to evaluate the risk of suicidality with the use of rimonabant, a specific analysis was performed by the Sponsor on the cases of suicide, suicide attempt, or suicide ideation reported as AEs or on associated symptoms of a psychiatric AE. In addition, an independent, blinded assessment was also performed by Columbia-Classification of Adult Suicidality Assessment (C-CASA) to identify definite cases (completed suicide, suicide attempt, preparatory acts toward imminent suicide behavior, suicidal ideation) and possible cases (not enough information fatal and non fatal).

From this analysis, no difference was observed when pooling all indications (obesity, smoking, alcohol, and schizophrenia). An imbalance was seen, however, in suicidal ideation in the obesity studies (0.63% in rimonabant versus 0.38% in placebo). All cases of suicidal ideation were associated with depressive events or adjustment disorders. Only one case was fatal (rimonabant 5-mg) assessed as a possible case (not enough information). This case had been reported as a completed suicide by the Investigator.

Section 7.5.1.2 details the C-CASA method of classification of cases according to the 9 categories of interest.

In the ongoing studies, the C-CASA was not yet applied. As of 01 March 2007 all cases of suicide and suicide attempts (as reported by the Investigator) were unblinded, 1 suicide was reported in a patient treated with rimonabant 20-mg and 2 suicide attempts in patients receiving placebo. The rate of suicidal ideation (0.3%) is similar to what was observed in completed studies. Around 40% of them were serious and unblinded. Among them an imbalance was observed (0.25% in rimonabant versus 0.11% in placebo). This trend is similar to that observed in the complete Phase 3 obesity studies.

Sanofi-aventis is proposing that rimonabant should not be initiated in patients with uncontrolled psychiatric illness such as a major depression. There is limited data in patients taking antidepressant medication in combination with rimonabant; therefore, the use of rimonabant is not recommended in these patients.

In addition to proposed labeling, sanofi-aventis is proposing a Risk Minimization Action Plan (Risk MAP) to reduce the possibility of rimonabant use inconsistent with the labeling in patients with diseases, conditions, or concomitant therapy that raise identified or potential safety concerns. This will be done by increasing the knowledge of key stakeholders (including prescribers/health care professionals, pharmacists, and patients) on the safety and efficacy profile of rimonabant through a Targeted Education and Outreach Program and a Reminder System. The overall Risk MAP effectiveness will be assessed periodically and further ongoing and iterative development is expected with

follow-up actions implemented, as needed. Details regarding the proposed Risk MAP are presented in Section 9 of this briefing package.

Neurological events

In general, neurological events occurred more frequently in the rimonabant groups when compared with the placebo groups. Events were classified in 3 main categories: sensory changes, motor impairments, and cognitive difficulties [Table (1.7) 8].

Table (1.7) 8 - Neurological AEs reported with an incidence of ≥1% in obesity studies

Neurological Symptoms	**Placebo (N=2474) N (%)**		**5 mg (N=2520) N (%)**		**20 mg (N=2742) N (%)**	
Any Class - any event	310	(12.5)	403	(16.0)	554	(20.2)
Sensory changes						
Any event	230	(9.3)	299	(11.9)	406	(14.8)
Dizziness	101	(4.1)	148	(5.9)	200	(7.3)
Paresthesia	22	(0.9)	25	(1.0)	41	(1.5)
Dysgeusia	6	(0.2)	6	(0.2)	8	(0.3)
Hypoesthesia	21	(0.8)	35	(1.4)	39	(1.4)
Sciatica	16	(0.6)	23	(0.9)	34	(1.2)
Motor impairment						
Any event	57	(2.3)	68	(2.7)	93	(3.4)
Tremor	2	(<0.1)	6	(0.2)	24	(0.9)
Cognitive difficulties						
Any event	51	(2.1)	66	(2.6)	113	(4.1)
Somnolence	5	(0.2)	12	(0.5)	14	(0.5)

Among sensory changes, dizziness was the most frequent event. Episodes of dizziness occurred in 7.3% of patients in the rimonabant 20-mg group compared to 4.1% of patients in the placebo group, generally during the first month following the first study drug intake. Reports of dizziness were more frequent in the rimonabant groups compared with the placebo groups for patients with type 2 diabetes mellitus (9.6% versus 4.3%, respectively) and in elderly patients (15.3% versus 2.7%, respectively). One case of dizziness was serious in the rimonabant 20-mg group and dizziness led to study drug discontinuation in 9% of patients in that group. These events were not associated with hypotension, hypoglycemia, or falls.

Paresthesia was a common AE among patients with type 2 diabetes mellitus (2.9% with rimonabant versus 0.6% for placebo).

Tremor was the most frequently reported AE within the motor impairment category. Tremor was reported with a higher incidence in the rimonabant 20-mg groups (0.9%) compared with the placebo group (<0.1%), occurred within the first 2 months of introduction of rimonabant, and resulted in treatment discontinuation in 20% of patients in the rimonabant 20-mg groups and none in the placebo groups.

Cognitive difficulties were more commonly reported with rimonabant compared to placebo (4.1% versus 2.1%, respectively, in obesity studies) and included somnolence/sedation/lethargy and memory loss (1.5% versus 0.7% in obesity studies). These events were more frequently described in the smoking cessation studies and could be linked to nicotine withdrawal. None of the cases were serious and they rarely led to treatment discontinuation for any of the treatment groups.

For patients receiving rimonabant in the Phase 3 obesity and smoking studies, 0.2% reported confusion or disorientation. Other neurological events were of various types and included ischemic or hemorrhagic cerebral stroke, localized motor deficits, or other atypical neurological signs. These reports were either isolated cases or reported in comparable proportions of patients across treatment groups, including the placebo group.

Seizures

Nonclinical studies suggest a weak proconvulsant potential for rimonabant when combined with pentylenetetrazole, which alone induces convulsions, or under stressful conditions (experimental procedures) in repeated-dose toxicity studies in some species. Due to its potential impact on the central nervous system (CNS), intensive electroencephalogram (EEG) monitoring was systematically performed throughout the Phase 1 clinical program. Results showed a comparable frequency of EEG changes in the rimonabant group compared with the placebo group.

In the Phase 3 clinical studies, patients with treated epilepsy were excluded. However, patients with a prior history of seizures were permitted. Rare cases of seizures were reported during the clinical development program (completed studies), regardless of the indication: placebo: 0.232% patient-years versus all doses of rimonabant: 0.158% patient-years [relative risk 0.68; CI (0.31, 1.51)].

Sanofi-aventis is recommending that rimonabant be used with precaution in patients with epilepsy. Results from non-clinical studies suggest that rimonabant has a weak proconvulsant potential when administered to animals, which is not confirmed in the clinical situation. A comprehensive evaluation of the available clinical data has shown that cases of seizures have been rarely reported in patients treated with rimonabant with no evidence of an increase in the seizure rate in patients treated with rimonabant 20-mg compared to placebo. Rimonabant has not been studied in patients being treated for epilepsy. Rimonabant should be used with caution in patients being treated for epilepsy.

In addition to proposed labeling, sanofi-aventis is proposing a Risk Minimization Action Plan (RiskMAP) to reduce the possibility of rimonabant use inconsistent with the labeling in patients with diseases, conditions, or concomitant therapy that raise identified or potential safety concerns. This will be done by increasing the knowledge of key stakeholders (including prescribers/health care professionals, pharmacists, and patients) on the safety and efficacy profile of rimonabant through a Targeted Education and Outreach Program and a Reminder System. The overall Risk MAP effectiveness will be assessed periodically and further ongoing and iterative development is expected with follow-up actions implemented, as needed. Details regarding the proposed Risk MAP are presented in Section 9 of this briefing package.

Other safety parameters

Standard laboratory tests did not provide evidence of safety concerns with respect to the main biological functions (liver, renal, hematology, electrolytes, and metabolism). Similarly, the review of vital signs [supine blood pressure (BP) and heart rate (HR)] did not raise any safety concerns. In the specific ECG Phase 1 study designed to evaluate the electrocardiographic safety of rimonabant, there was no evidence of a potential for rimonabant to prolong ventricular repolarization. Extensive ECG records from the Phase 3 studies confirmed these observations.

In conclusion, the safety of rimonabant has been characterized by the completion of the development program in obesity and patients with type 2 diabetes mellitus. Additional safety information was obtained from the studies conducted in smoking cessation. Based on these trials, the most frequently reported adverse reactions were of GI, nervous system, or psychiatric origin. Adverse events of interest have been identified and are being closely monitored and assessed in both the ongoing studies with rimonabant, as well as from the post-marketing surveillance reports from countries where the drug is currently marketed. A risk management plan has been instituted in the European Union and proposed in the US to facilitate both minimization and management practices in order to provide the greatest benefit to patients prescribed rimonabant.

1.8 Post-marketing experience

In June 2006, the European Medicines Evaluation Agency (EMEA) approved rimonabant for marketing authorization under the trade name ACOMPLIA®. As of April 2007, ACOMPLIA has been launched in the following countries: Argentina, Austria, Chile, Columbia, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Mexico, Norway, Sweden, and the United Kingdom (UK). A total of 108 730 people have been prescribed rimonabant in these countries as of 01 March 2007.

In addition, rimonabant has received marketing authorization but has not yet been launched in Belgium, Brazil, Bulgaria, the Czech Republic, Estonia, Guatemala, Hong Kong, Hungary, Italy, Kuwait, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Switzerland, the United Arab Emirates, and the Ukraine.

Assessment of drug risks and benefits starts during drug development and continues as part of risk management/minimization as the drug product moves out of the development stage. At product approval, the company works with the relevant regulatory authorities on product labeling that describes the conditions for safe and effective use of the drug. Product labeling is the basis for further risk management activities as the drug is marketed.

Based on a thorough review of all available preclinical and clinical safety data from the premarketing studies, sanofi-aventis developed a risk management plan (RMP) in Europe to monitor and manage identified and potential risks. Agreed upon by the EMEA, the first European RMP (EU-RMP) was dated 22 June 2006.

Preliminary results available on the EU-RMP from the European countries that have launched rimonabant indicate that the drug is used consistent with product labeling in more than 95% of the cases.

1.8.1 US proposed Risk Management Plan

In the US, sanofi-aventis is proposing a risk management plan to minimize identified and potential important risks, with particular emphasis on exposure of the drug to patient populations or conditions where patient safety risks may exist, or where safety information is not complete. In addition, since obesity is a chronic disorder, short term use is not recommended and the company does not intend to promote the product for short term cosmetic use. The risk minimization activities that have been launched successfully in the European Union will serve as the foundation to the RiskMAP proposed in the US. Sanofi-aventis is committed to providing information to key stakeholders (eg, healthcare prescribers, pharmacists, and patient) on the safety and efficacy profile of ZIMULTI® (rimonabant) and use of the drug consistent with product labeling and risk minimization.

The overall strategy proposed in the US RiskMAP is to accomplish risk minimization through a Targeted Education and Outreach Program and a Reminder System using some of the tools described later in the briefing package. The effectiveness of the proposed RiskMAP will be assessed periodically and the RiskMAP will be subject to ongoing and iterative development. Details regarding the proposed US RiskMAP are provided in Section 9.0 of this briefing package.

1.9 Benefit-risk ratio assessment

The efficacy and the safety of rimonabant in obese and overweight patients with cardiovascular risks were demonstrated in 4 adequate and well-controlled studies with reproducible results, and sustained over time, for up to 1 year (in all 4 studies) and 2 years (in 2 studies). In type 2 diabetic patients, 2 studies were conducted: RIO-Diabetes in patients not adequately controlled by single oral antidiabetic agent and SERENADE in drug naive patients. The 2 studies demonstrated that rimonabant 20-mg significantly decreases HbA_{1c} values compared to single oral antidiabetic agents or placebo. The 20-mg dose of rimonabant had favorable metabolic effects including improved insulin sensitivity,

increased HDL-C and decreased TG, and improved glucose control in type 2 diabetes, above and beyond its effect on body weight loss. Based on this body of data, rimonabant used in conjunction with a reduced calorie diet and physical exercise will be an important option in the management of obese and overweight patients with associated cardiovascular risk, including patients with type 2 diabetes.

Despite all efforts from the medical community and patients to fight the obesity epidemic using diet, counseling, and approved and non approved drugs, there is still a medical need for effective new pharmacotherapies that can help to achieve significant body weight loss and prevent short term relapse. Meaningful mean body weight loss, confirmed by the 2-to 3-fold higher rate of 5% and 10% responders compared with diet alone, observed after 1 year, demonstrates that rimonabant 20-mg results in sustained body weight loss and waist circumference reduction. Severe obesity (BMI of 40.0 kg/m^2 or higher) is increasing much faster than obesity, leading to more and more bariatric surgery and its related morbidity/mortality. Rimonabant 20-mg almost halved the percentage of patients with severe obesity after 1 year of treatment. One patient out of 4 lost more than 10% of their baseline body weight, tripling the effect of the diet. In severely obese patients, rimonabant demonstrated improvements in lipids and glucose/insulin homeostasis similar to the improvements seen in non-severely obese patients.

In 1996, the FDA published the draft guidance for the Clinical Evaluation of Weight-Control Drugs. This guidance outlined the criteria for regulatory approval for drugs to treat obesity, which included a minimum of one year of placebo-controlled exposure in 1500 patients and a second year of exposure in up to 500 patients. The efficacy criteria established by the guidance stipulated that the mean weight loss be 5% greater in drug versus placebo-treated patients or, that the proportion of patients losing 5% of their weight be greater in the drug versus placebo-treated group. Additionally, the populations to be studied in these trials were recommended to be patients with a body mass index (BMI) greater than 30 or greater than or equal to 27 with comorbidities such as hypertension, type 2 diabetes, and dyslipidemia. Earlier this year, the FDA published for public review and comment, a revised draft guideline entitled: Developing Products for Weight Management. The rimonabant development program has met the safety and efficacy criteria outlined in both the 1996 and the 2007 draft guidance documents.

Additionally, in 1998-2000 the NIH established clinical guidelines for the treatment of overweight and obesity. In addition to establishing a BMI classification based on epidemiology data that showed increases in mortality with BMIs greater than 25, the guidelines also stated that “weight loss medications should be used only by patients who are at increased medical risk because of their weight and should not be used for cosmetic weight loss.” Furthermore, weight loss medications should never be used without concomitant lifestyle modifications. Importantly, the guidelines also recognized that obesity is a chronic disorder (disease) and that short-term treatment with anti-obesity pharmacotherapy is not helpful. Rimonabant has been developed for those patients at increased medical risk due to their overweight or obesity. Rimonabant, in combination with lifestyle modifications, provides a medical therapy for a chronic disease.

Both the American Heart Association (AHA) and American Diabetes Association (ADA) emphasize the importance of weight management in cardiovascular risk including diabetes. Thus, there is a need for treatment of type 2 diabetic patients that will not only lower HbA_{1c}, but will also decrease body weight and the metabolic disorders associated with excess weight. The RIO-Diabetes study in treated type 2 diabetic patients showed that rimonabant, at the dose of 20-mg once daily, could accomplish these goals, when diet plus the single agent (metformin or sulfonylureas) did not result in adequate glycemic control. The 0.7% decrease in HbA_{1c} over the placebo effect, with 67.9% of patients reaching an HbA_{1c} level <7% demonstrated a significant improvement in glucose control. The 6-month SERENADE study in treatment-naive type 2 diabetic patients confirmed the benefits seen with rimonabant in the 12-month RIO-Diabetes study. The SERENADE study showed a placebo-adjusted decrease in HbA_{1c} of 0.5% in the overall population and a 1.2% decrease in patients with a baseline HbA_{1c} above 8.5%. About one-half of the benefit was beyond what was expected from weight loss alone. Moreover, the 4.0 kg (8.8 lbs) placebo-adjusted weight loss and the 3.7 cm decrease in waist circumference point toward a reduction in cardiovascular risk. Thus, both the RIO-Diabetes and SERENADE studies showed that rimonabant significantly improves glycemic control in type 2 diabetic patients, with significant body weight loss and a positive impact on the lipid profile, a triple benefit that should be considered a very important addition to the currently available treatments, and in direct contrast to the majority of anti-diabetic treatments that increase body weight. These results suggest that the addition of 20-mg rimonabant to metformin or sulfonylurea appears as an effective therapeutic option for the management of patients with type 2 diabetes.

The safety profile of rimonabant was documented by a database comprising the obesity and diabetes programs, including more than 13 000 individuals treated, contributing more than 3000 patient-years of experience at the 20-mg dose. A similar safety profile was observed between the obesity and diabetes populations with GI events (such as nausea, vomiting, and or diarrhea) psychiatric disorders (such as insomnia, anxiety, depressive mood disorders, and disturbances), and nervous system disorders (such as dizziness) were being reported in rimonabant-treated patients.

Anxiety, depressed mood, depressive disorders, and dizziness, were observed in the 20-mg rimonabant group, and were usually mild and transient. The discontinuation rate due to depressive disorders, in part, reflects the protocol mandate for discontinuation when antidepressive therapy was required due to the confounding effect of antidepressants on body weight. Based on this safety experience, therapy with rimonabant should not be initiated in patients with uncontrolled serious psychiatric illness such as a major depression. Appropriate treatment of this condition should be initiated first and therapy with rimonabant considered once this psychiatric condition is controlled and the patient is no longer taking antidepressant medication. As there is limited data in patients with antidepressant medication in combination with rimonabant, use of rimonabant is not recommended in these patients. In type 2 diabetes, rimonabant was well tolerated with a somewhat greater incidence of paresthesia. Importantly, there was a low risk of hypoglycemia, a finding of particular interest for use in patients already on medications that have such adverse reactions.

Dizziness, paresthesia, hypoesthesia, and with a less frequency tremor, memory impairment, confusion, and disorientation all occurred in a small number of patients more frequently in the rimonabant 20-mg group than in the placebo group. No serious neurological AEs occurred that were related to rimonabant treatment. A total of 3 (2 during rimonabant 5-mg treatment; 1 during placebo) cases of multiple sclerosis were reported in the clinical development program. No cases were reported in the rimonabant 20-mg group or during the second year of exposure. In addition, 1 patient in the 20-mg group with a medical history of multiple sclerosis presented an episode of diplopia related to his preexisting disease.

Seizures were reported in all treatment groups, with a low and similar frequency with rimonabant and placebo.

In conclusion, the benefit-risk ratio of rimonabant at the dose of 20-mg once daily is favorable in the obese, overweight, and diabetes populations. By directly addressing a dysfunctional endocannabinoid system, rimonabant addresses the root causes of the disease, (ie, abdominal obesity and insulin resistance). Especially for patients with type 2 diabetes, the benefit-risk ratio is particularly favorable: rimonabant improves glucose control, decreases body weight, and improves the lipid profile in a situation of inadequate glucose control with an oral antidiabetic drug that would then lead to the addition of treatments, generally further increasing body weight and failing to control the dyslipidemia of diabetes.

The overall benefits in body weight, waist circumference, and metabolic parameters seen in all patient populations studied outweigh the risks that are manageable in clinical practice. Prospective steps to minimize the known risks and manage these risks in clinical practice are critical for the successful use of rimonabant in the appropriate patient populations.

2. PROPOSED INDICATIONS

Based on the safety and efficacy data from the completed Phase 3 studies, sanofi-aventis has proposed the following indications for rimonabant:

- ZIMULTI® is indicated as an adjunct to diet and exercise for the treatment of overweight patients with BMI >27 kg/m^2 and at least 1 other cardiovascular risk factor, or for the treatment of obese patients with a BMI ≥30 kg/m^2;
- ZIMULTI® is also indicated in combination with metformin or a sulfonylurea to improve glycemic control and reduce weight in patients with type 2 diabetes and a BMI >27 kg/m^2 when diet and exercise plus a single agent do not result in adequate control.

3. EPIDEMIOLOGY OF OBESITY AND TYPE 2 DIABETES MELLITUS

3.1 Obesity

3.1.1 Prevalence

Based on results from the National Health and Nutrition Examination Survey (NHANES), the prevalence of the "overweight" condition increased 8% between NHANES II (1976 to 1980) and NHANES III (1988 to 1991) among US adults 20 to 74 years-of-age (1). Results from NHANES III showed that 33.4% of US adults were overweight (BMI ≥27.8 kg/m^2 for men and ≥27.3 kg/m^2 for women).

A more recent study showed that the prevalence of obesity (BMI ≥30 kg/m^2) in US adults (aged 20 years or older) was 30.5% from 1999 to 2000 and 30.6% from 2001 to 2002 (2). The prevalence of overweight or obesity (BMI ≥25 kg/m^2) in US adults (20 years of age or older) was 64.5% from 1999 to 2000 and 65.7% from 2001 to 2002 (2). The prevalence of obesity has increased over time, especially in the last 2 decades (3). An increase in the prevalence of obesity has been observed, not only in the US, but also in countries in Europe and around the world (4),(5),(6),(7),(8),(9).

According to International Obesity Task Force (IOTF) data (10), the prevalence of overweight (BMI: 25 to 29.9 kg/m^2) in European countries ranged from 32% to 57% in males and from 23.3% to 56.0% in females. Similarly, the prevalence of obesity (BMI ≥30 kg/m^2) varied in males (9.3% to 26.6%) and in females (8.7% to 35%).

3.2 Diabetes mellitus

3.2.1 Incidence

Obesity has been associated with an increased incidence of type 2 diabetes, as shown in US studies (11),(12). Among more than 37 000 women participating in the Women's Health Study (6.9 years of follow up), obesity was associated with an increased incidence of type 2 diabetes with a hazard ratio of 9.06 (95% CI, 7.60-10.80), following adjustment for age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and physical activity (11). Results from this study were confirmed by those from the Health Professional Follow-up Study (12). In this study, approximately 51 000 male health professionals 40 to 75 years of age in 1986 who were free of diabetes at baseline were followed for 5 years. Obesity was associated with an increased incidence of noninsulin-dependent diabetes mellitus with a relative risk of 42.1 (95% CI, 22.0-80.6) for BMI ≥35 kg/m^2 (reference, BMI <23 kg/m^2) (12).

A longitudinal population-based study in Italy (13) showed that the incidence rates of diabetes mellitus were approximately 3-fold higher in individuals with a BMI ranging from 25 to 30 kg/m^2 (10.8 per 1000 person-years) versus those with BMI <25 kg/m^2 (4.1 per 1000 person-years) and was approximately 10-fold higher in obese individuals. Otherwise, an increase in BMI ≥2 kg/m^2 in the period 1990 to 1995 was associated with

an increased risk of diabetes with an odds ratio of 2.2 when compared with a stable BMI. In a Finnish study (14), the relative risk of diabetes rose greatly with increasing BMI for both men [from 2.53 (for BMI of 27.1 to 28.9 kg/m^2) to 27.9 (for BMI of ≥35 kg/m^2)] and women [from 5.6 (for BMI of 27.1 to 28.9 kg/m^2) to 11.07 (for BMI of ≥35 kg/m^2)]. Another study among the Finnish (15) showed that the adjusted hazard ratios for the risk of diabetes based on 3 ranges of BMI values (<25, 25 to 29.9, and ≥30 kg/m^2) were 1.00, 1.79, and 6.25, respectively. In a UK prospective study (16), BMI was the dominant risk factor for diabetes with an age-adjusted relative risk of 11.6 (upper fifth-BMI ≥27.9 to lower fifth-BMI ≤22.9 kg/m^2).

3.2.2 Prevalence

The prevalence of diagnosed and undiagnosed diabetes (fasting plasma glucose of at least 126 mg/dL) in the US population 20 years of age or older from 1988 to 1994 (NHANES III) was 7.8% (17). A more recent study based on the NHANES 1999-2002 data showed that the prevalence of diabetes in the US aged 20 years or older from1999-2002 was 9.3% (19.3 million subjects based on US 2000 Census); 6.5% diagnosed and 2.8% undiagnosed diabetes (18). The prevalence of diabetes increased with age.

The prevalence of diabetes also increased over time. In a recent NHANES (1999 to 2000) study, Cowie et al showed that the prevalence of total diabetes (diagnosed and undiagnosed diabetes combined) during 1999 to 2000 was 8.3%. The discrepancies in prevalence across age, sex, and ethnicity groups were similar to those for diagnosed diabetes (19).

Based on data from The National Health Examination Survey (NHES) and a series of NHANES conducted from 1960 to 1962 (NHES), 1971 to 1975 (NHANES I), 1976 to 1980 (NHANES II), 1988 to 1994 (NHANES III), and 1999 to 2000 (NHANES 1999 to 2000), Gregg et al showed that there was a relationship between BMI level and the age-adjusted prevalence of diagnosed and undiagnosed diabetes in the US population 20 years of age or older (20). This study also showed that, between 1960 and 1962 and 1999 and 2000, the prevalence of diagnosed diabetes in the US population increased from 1.8% to 5.8%. The greatest increase, from 4.9% to 15.1%, was among subjects with a BMI over 35 kg/m^2.

4. MECHANISM OF ACTION

4.1 Overview of the endocannabinoid system

4.1.1 Description and function of the endocannabinoid system

The ECS comprises 2 receptors (CB_1 and CB_2), endogenous lipid signaling molecules ("endocannabinoids") anandamide and 2-arachidonoyl-glycerol (2-AG) (21), and the enzymes involved in their synthesis (NAPE-phospholipase D) and degradation (fatty acid amide hydrolase [FAAH], and monoglycerol lipase). The CB_1 subtype is distributed in the brain and in peripheral organs and tissues. In the brain, endocannabinoids act as retrograde neuro-transmitters, synthesized in response to postsynaptic membrane depolarization and released by postsynaptic neurons, migrating in retrograde fashion to an adjacent presynaptic membrane where they activate CB_1-receptors and inhibit neurotransmitter release before rapid degradation. Beyond this role of neuromodulation of synaptic transmission, the ECS is also involved in regulation and integration of central behavioral aspects of nutrient intake plus the peripheral modulation of nutrient transport, metabolism, and storage via direct activation of CB1 receptors located in the GI tract, liver, adipose tissue, muscle, and pancreas (22).

4.1.2 Role of the ECS in the regulation of ingestive behavior

Endocannabinoids interact with hypothalamic circuits to stimulate food intake, and in reward areas of the brain such as the nucleus accumbens in the mesolimbic system to selectively enhance intake of palatable foods (23),(24),(25). In fact, preclinical reports have shown that 1) feeding lowers, and fasting raises, hypothalamic, but not cerebellar, levels of the endocannabinoid 2-AG (26); 2) CB_1-receptor deletion blunts refeeding in fasted animals (27); and 3) local injection of endocannabinoids into the hypothalamus or nucleus accumbens stimulates feeding in satiated animals, an effect which is blunted by CB_1-receptor blockade (28).

4.1.3 Role of the ECS in peripheral energy storage and metabolism

Identification of CB_1 receptors in the GI tract, liver, adipose tissue, muscle, and pancreas has also been recently reported (22). Local stimulation of CB_1 receptors in the GI tract promotes hyperphagia (29). In the adipose tissue, CB_1 receptor stimulation induces lipoprotein lipase, a key enzyme regulating adipocyte fat accumulation, and cellular hypertrophy (24), while repressing adiponectin gene expression (30), an effect that translates into decreases in circulating plasma adiponectin levels (31). In view of the established protective role of adiponectin against insulin resistance, diabetes, and atherosclerosis, the ECS-induced inhibition of adiponectin could be an important peripheral mechanism contributing to obesity-related metabolic and cardiovascular complications (31),(32),(33),(34),(35). In the liver, activation of the CB_1 receptor increases expression of lipogenic enzymes and inhibits fatty acids oxidation (10) while in skeletal muscle, it decreases glucose uptake (22). Globally, the activation of the ECS in peripheral tissues favors fat storage in adipose tissue and liver to the detriment of its metabolic consumption.

4.2 Over activation of the ECS in obesity - evidence from animal models

4.2.1 Hypothalamic ECS dysregulation

In animal models such as obese db/db or ob/ob mice and Zucker rats, hypothalamic endocannabinoid levels are paradoxically elevated despite hyperphagia (24),(27). Moreover, these animals develop resistance to the physiological control of feeding by leptin and insulin, while in normal animals, leptin administration lowers hypothalamic endocannabinoid levels (27).

4.2.2 Peripheral ECS dysregulation

The central ECS over activation observed in genetic and diet-induced obesity models is mirrored in peripheral tissues with increased endocannabinoid production in adipocytes, hepatocytes, and pancreatic cells derived from obese versus lean rodents and increased CB_1-receptor expression in adipose tissue, liver, and skeletal muscle (30),(31),(36),(37). In the liver, over activation of ECS leads to shifting the balance of fatty acid oxidation and synthesis in the direction of increased hepatic fat accumulation and hepatic insulin resistance, and potentially enhancing very low-density lipoprotein (VLDL) production and triglyceride flux (37). The overall consequences of ECS over activation in animal models of obesity consist of dysregulation of lipid and glucose metabolism, glucose intolerance (33), and abnormal serum lipid profiles (30).

4.3 Consequences of blockage of the ECS over activation

4.3.1 Effects of rimonabant on ingestive behavior and body weight

Rimonabant specifically reduced the over consumption of palatable diet or drinks in rats and marmosets (25),(38), with weak effects on standard diet. Rimonabant also counteracted the pharmacologically or genetically-induced hyperphagia in various rat models. The anti-obesity effects of rimonabant have been confirmed in a variety of animal models including congenital obesity, obese Zucker rats, and in high-fat diet induced obesity (DIO) in C57BL/6 mice (39). Rimonabant had no effect on food intake or body weight in CB_1 knockout mice fed a high-fat diet, confirming that its effects are indeed mediated by the CB_1 receptor (22),(23),(24),(39).

4.3.2 Effects of rimonabant on metabolism in peripheral tissues and organs

Observations that genetic deletion or pharmacological CB_1-receptor blockade produced a sustained reduction in body weight beyond that attributed to the transient reduction in food intake, and the persistently lower body weight of rimonabant-treated versus pair-fed controls (around 50%) implicated the ECS in peripheral metabolic processes other than central regulation of feeding behavior. These peripheral effects are described in Table (4.3.2) 1. In aggregate, these examples represent the critical involvement of the ECS in numerous physiological pathways and reflect the ECS dysregulation noted in a variety of genetic and experimentally induced animal models of obesity, insulin resistance, and dyslipidemia. This link between ECS dysregulation and metabolic sequelae provides a plausible biological foundation for peripheral metabolic effects above and beyond those attributable to changes in body weight and highlight the ECS as a therapeutic target.

Table (4.3.2) 1 - Observed effects of CB_1 receptor blockade and potential consequences of reducing ECS over activity in obesity and related metabolic disorders

Site of action	Biological effects	Pathological consequences	References
White adipose tissue	↓ Expression of LPL ↓ HFD-induced changes in gene expression ↑ Lipolysis by induction of β-oxidation & TCA cycles ↑ Energy expenditure through futile cycling and GLUT-4 ↑ Adiponectin mRNA & protein in cultured adipocytes ↑ Adiponectin production and release	↓ Lipogenesis ↑ Lipolysis ↓ Body weight ↑ Fatty acid oxidation ↑ Insulin sensitivity ↓ Atherogenic lipid profile	(24) (40) (30)
Pancreas	Delay development of hyperinsulinemia with no effect on basal glycemia in obese Zucker rats ↓ Insulin secretion in static incubation in response to low &high glucose stimulation ↓ Hyperplasia and destructuration of islets with no effect on islet number	↑ Insulin sensitivity Protective effect on pancreatic function	(MVV0001) (MVT0009)
Skeletal muscle	↑ Glucose uptake ↑ Oxygen consumption	↑ Insulin sensitivity ↑ Glycemic control ↑ Thermogenesis	(32),(33)
Liver	↓ ALT, GGT, ALP (liver injury enzymes) ↓ TNFα	↓ Hepatic steatosis ↓ Hepatomegaly ↓ Hepatic fat infiltration	(NVV0402)
Gastrointestinal tract	↓ Rise in ghrelin	↓ Peripheral orexigenic signal	(41)
Hypothalamus	↓ Food intake in food-deprived rats and partially satiated rats when administered intraperitoneally (IP)	↓ Feeding through CB_1 crosstalk with orexigenic signals originating in the GI tract	(29)

[a] Upward arrows indicate upregulation or stimulation, and down ward arrows indicate down regulation or inhibition. Abbreviations:, high-density lipoprotein (HDL); very low-density lipoprotein (VLDL); glucose transporter-4 (GLUT-4); alanine aminotransferase (ALT), gamma glutamyl transferase (GGT); tumor necrosis factor α (TNFα); alkaline phosphatase (ALP)

4.4 Evidence linking ECS dysregulation to obesity in humans

Several lines of clinical evidence implicate ECS dysregulation in the pathophysiology of human obesity (21). These include the population association of a genetic polymorphism encoding a missense mutation in FAAH, the enzyme that degrades anandamide, with increased BMI, and biochemical evidence of increased blood levels of endocannabinoids and reduced adipocyte FAAH expression in obese versus lean patients and type 2 diabetes versus nondiabetic patients (34),(42),(43),(44),(45). Blood anandamide and 2-AG levels were higher in 20 obese patients compared to 20 lean controls with similar demographic and clinical characteristics (31). Moreover, in a cohort of obese patients, endocannabinoid levels remained elevated after mild weight loss, suggesting that chronically increased endocannabinoid levels are an intrinsic characteristic of the obese state rather than simply an acute response to overeating (42). Higher circulating endocannabinoid levels have also been noted in patients with type 2 diabetes compared with nondiabetics (34). Two recent studies demonstrated increased circulating endocannabinoid levels in the obese phenotype characterized by excess abdominal visceral fat content compared with both nonobese patients and comparably obese patients with a predominance of either excess subcutaneous or excess lower body adipose tissue (44),(45). Furthermore, there are differences in the activity of the ECS between human visceral and subcutaneous depots with higher 2-AG levels in omental adipose tissue compared with subcutaneous fat (34). These observations suggest that dysregulation of the ECS may contribute to the established association between predominantly excessive visceral adipose tissue and elevated cardiovascular and metabolic risk factors, such as dyslipidemia and insulin resistance. These new results in human obesity and type 2 diabetes support the relevance and clinical translation of preclinical findings of central and peripheral ECS upregulation to man, and confirm the biologic basis for weight-independent as well as weight-dependent effects of the CB_1 blockade with rimonabant in obese and diabetic patients [Table (4.3.2) 1].

5. PHARMACOKINETICS

5.1 Absorption, distribution, metabolism, and elimination

The pharmacokinetic profile of rimonabant is characterized by a rapid absorption, a high and nonsaturable plasma protein binding (mainly to albumin), CYP3A- and amidohydrolase-mediated metabolism, and elimination mainly by the liver [Table (5.1) 1].

Table (5.1) 1 - Rimonabant pharmacokinetic characteristics

Process	**Parameter**	**Value**
Absorption	Permeability and transport in vitro Effect of food	High, with no P-gp transport Increase in C_{max} (67%) and AUC (48%)
Distribution	Binding to plasma proteins in vitro	>99%
Metabolism	Enzyme Circulating metabolites	CYP3A (f_m up to 60%) and amidohydrolases SR141715 (acid derivative), SR142923 (hydroxy derivative on piperidine), SR90161 (propionic acid derivative of SR142923), none of which contribute to pharmacological activity
Elimination	Terminal half-life Fecal recovery Urinary recovery	6 – 9 days (non-obese); 16 days (obese) ~ 86% of the administered dose 3% of the administered dose
Other	Steady-state C_{max} (Mean±SD, 20-mg) Steady-state C_{trough} (Mean±SD, 20-mg) Steady-state t_{max} (Median) Steady-state AUC_{0-24} (Mean±SD, 20-mg) Time to steady-state (Median) Accumulation Dose proportionality	196 ± 28.1 ng/mL 91.6 ± 14.1 ng/mL 1 to 3.75 h 2960 ± 268 ng.h/mL 13 days (non-obese); 25 days (obese) 3.3 fold Near dose proportional exposure increase up to 20-mg and then less than dose proportional increase; mean exposure plateau at about 180 mg in a single dose study

5.2 Special populations

Of the various intrinsic factors investigated, only race, age, and body weight had an effect on rimonabant pharmacokinetics [Table (5.2) 1]. Population pharmacokinetic analysis predicted lower exposure in black patients (due to higher clearance) compared to patients of other races, higher exposure in elderly patients (due to lower clearance) relative to young patients, less peak-to-trough concentration fluctuations, and a longer half-life (due to higher peripheral volume of distribution) in more obese patients than less obese patients.

Table (5.2) 1 - Rimonabant pharmacokinetics in special populations

Factor	**Effect**
Race	Lower C_{max} (31%) and AUC (43%) in Black patients than others[a]; no difference between Japanese and Caucasian subjects[b]
Age	Higher C_{max} (21%) and AUC (27%) in elderly than young patients[a]
Body weight	Lower C_{max} (24%) and higher C_{trough} (5%), but no effect on AUC, with increase in weight from 65 kg to 200 kg[a]
Gender	No effect[a]
CYP2D6, 2C9, 2C19 phenotype	No effect[c]
Smoking	No effect[a]
Hepatic impairment (mild, moderate)	No effect[b, d]
Renal impairment (mild, moderate)	No effect[a]

[a] Based on population pharmacokinetic analysis of Phase 3 patient data.
[b] Specific Phase 1 study.
[c] Based on metanalysis of data pooled from several Phase 1 studies in healthy subjects.
[d] Effect of severe hepatic impairment not assessed.

5.3 Drug-drug interactions

Of the various drug-drug interactions studied, moderate and potent inhibitors of CYP3A increased rimonabant exposure. Caution is advised during concomitant use with potent CYP3A inhibitors (eg, ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, nefazodone). Although the effect of CYP3A inducers (eg, rifampicin, phenytoin, phenobarbital, carbamazepine, St John's Wort) has not been studied, it is expected that concomitant administration of potent CYP3A inducers may reduce the plasma concentrations of rimonabant and may result in loss of efficacy.

Based on its lack of CYP or P-gp inhibition/induction potential, a pharmacokinetic effect of rimonabant on frequent concomitant medications such as lipid lowering agents, antidiabetic agents, or antihypertensive agents, is not expected.

Table (5.3) 1 - Drug-drug interactions

Mechanism	Interacting Drug (Dose)	Substrate (Dose)	Substrate Ratio (90%CI) [a]	
			C_{max}	AUC
Effect of other drugs on rimonabant				
CYP3A inhibition	Ketoconazole (400 mg QD)	Rimonabant (20-mg)	1.24 (1.05-1.46)	2.72 (2.45-3.02)
	Ketoconazole (200 mg QD)	Rimonabant (20-mg)	1.42 (1.18-1.70)	2.04 (1.89-2.23)
	Diltiazem (240 mg QD)	Rimonabant (20-mg)	1.35 (1.18-1.56)	2.02 (1.89-2.17)
Other	Orlistat (Xenical) (120-mg TID)	Rimonabant (20-mg)	0.72 (0.55-0.94)	No effect
	Alcohol (0.7 g/Kg)	Rimonabant (20-mg QD)	No effect[b]	
	Lorazepam (2 mg)	Rimonabant (20-mg QD)	No effect[b]	
Effect of rimonabant on other drugs				
CYP3A inhibition or induction	Rimonabant (40 mg QD)[c]	Midazolam (0.03 mg/kg)	No effect	No effect
		Ethinylestradiol (0.03 mg QD)	1.21 (1.10-1.34)	No effect
		Levonorgestrel (0.15 mg QD)	No effect	No effect
CYP2C9 inhibition or induction	Rimonabant (40 mg QD)[c]	Warfarin (30 mg)	No effect	No effect
Pgp inhibition	Rimonabant (40 mg QD)[c]	Digoxin (0.5/0.25 mg QD)	No effect	No effect
Other	Rimonabant (40 mg QD)[c]	Nicotine (21 mg QD), and cotinine (metabolite)	No effect	No effect

[a] (coadministered treatment)/(reference treatment alone) ratio for substrate C_{max} or AUC (extrapolated to infinity for a single dose or over 24 h for repeated doses)

[b] Assessment based on C_{trough} of rimonabant as full pharmacokinetic profiles were not obtained

[c] Rimonabant 40 mg QD administered for 8 days to reach/exceed steady state exposure at 20-mg QD once a day (QD); three times a day (TID)

5.4 Pharmacokinetic/pharmacodynamic relationship

In the obesity trials, there was a dose-effect relationship with a corresponding exposure (C_{trough}) effect relationship on weight loss. A relationship between exposure and common AEs (such as nausea, vomiting, etc) was also observed in these studies.

6. CLINICAL EFFICACY

6.1 Obesity

Four Phase 3 trials were initiated between August and December 2001 in 14 countries, involving North America and Europe, Argentina, and Australia (46),(47),(48),(49). All studies were double-blind and placebo-controlled, with 3 parallel-treatment groups, where rimonabant 5-mg or 20-mg or placebo were given once daily. All studies used a 2-week screening period and a 4-week run-in period.

RIO-Europe and RIO-North America enrolled overweight adult patients (BMI >27 kg/m²) with at least 1 comorbidity (hypertension or dyslipidemia) and obese patients (BMI ≥30 kg/m²) with or without comorbidities. For the RIO-Lipids study, patients

eligible for inclusion were overweight or obese adults (BMI 27 to 40 kg/m^2) under 70 years of age with untreated dyslipidemia, defined as TG ≥1.69 mmol/L or a ratio of total cholesterol to HDL-C >4.5 in women or >5 in men. For the RIO-Diabetes study, patients eligible for inclusion were overweight or obese adults (BMI 27 to 40 kg/m^2) under 70 years of age inadequately controlled with metformin or sulfonylurea monotherapy for at least 6 months. Patients were excluded if they had a prior history of depression necessitating hospitalization, 2 or more recurrent episodes of depression, or a suicide attempt. Concomitant use of medications known to alter body weight or appetite, including anti-obesity drugs, corticosteroids, antidepressants, neuroleptics, nonselective systemic antihistamines, and nicotine substitutes, were not permitted.

After initial screening, all patients entered a 4-week, single-blind run-in period during which a reduced hypocaloric diet (to achieve a 600 kcal/day deficit) was prescribed following an interview with a dietitian. In addition, patients were advised to increase their physical activity levels. At the end of the run-in period, eligible patients were randomly allocated to daily treatment with either rimonabant (5-mg or 20-mg) or placebo for 1 year. The randomization ratio (placebo:rimonabant 5-mg:rimonabant 20-mg) in RIO-Europe and RIO-North America was 1:2:2 and in RIO-Lipids and RIO-Diabetes, it was 1:1:1. Patients who completed 1 year of treatment in RIO-North America were re-randomized to placebo or rimonabant for the second year of treatment [Figure (6.1) 1].

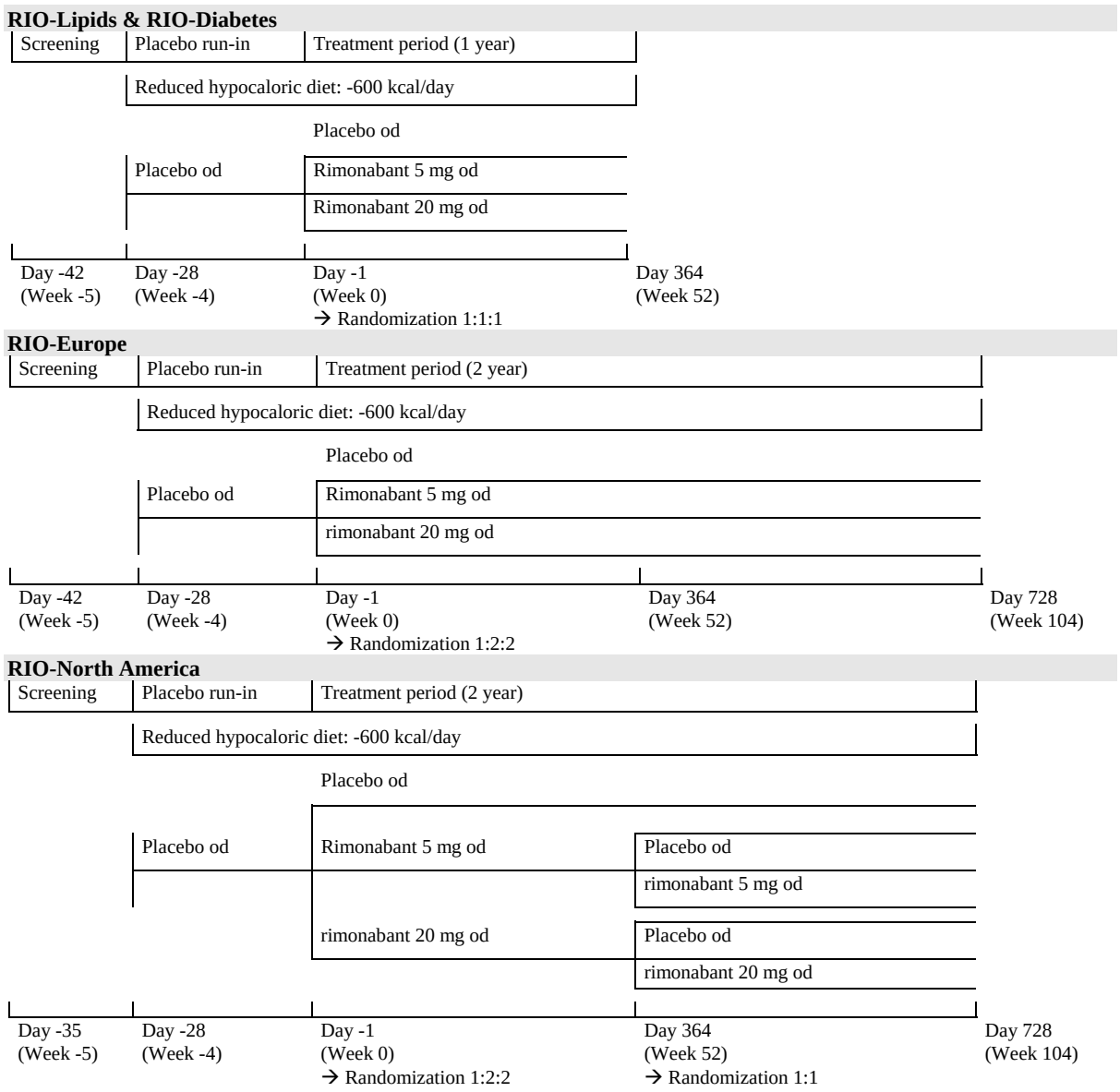

Figure (6.1) 1 - Design of the 4 Phase 3 studies (RIO studies)

Treatment visits took place monthly during the treatment period, and standardized assessments of body weight, blood pressure (BP), waist circumference, smoking status, and concomitant medications were performed at each visit. In addition, patients received dietary counseling and were encouraged to increase their physical activity levels.

Lipid profile, fasting glucose, and fasting insulin were measured every 3 months by the use of standard procedures in a central laboratory (ICON Laboratories, Farmingdale, NY, USA and Dublin, Ireland). Changes in insulin resistance were derived from the homeostasis model assessment (HOMA-IR), which was calculated as fasting insulin (µU/mL) × fasting glucose (mmol/L)/22.5. The prevalence of metabolic syndrome was assessed at baseline and at 1 year according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (50).

Populations and endpoints

A total of 3045 patients were enrolled in RIO-North America, 1036 in RIO-Lipids, 1508 in RIO-Europe, and 1047 in RIO-Diabetes.

Efficacy analyses were performed on the intent-to-treat (ITT) and completer populations; safety analyses were performed on the randomized and exposed patient population (safety population). The ITT population included all randomized patients who received at least 1 dose of double-blind study drug, had at least 1 postbaseline assessment, and, where appropriate, a baseline assessment. The completer population included all patients in the ITT population who completed the last scheduled visit during the treatment period without definitive treatment discontinuation. The safety population included all randomized patients who received at least 1 dose of double-blind study drug.

The primary efficacy endpoint in all RIO studies was weight loss after 1 year of treatment in the ITT population; it was assessed as the absolute change in weight from baseline to 1 year. In RIO-North America, the primary endpoint of the second year was body weight regain at 2 years; it was assessed as the absolute change in weight from the end of the first year to the end of the second year. These studies had similar confirmatory secondary endpoints: percent change in HDL-C at 1 year in all 4 studies, TG in 3 of 4 studies, and change in oral glucose tolerance test (OGTT) at 1 year in 2 studies, where change was assessed as the improvement in glucose tolerance among patients with impaired or diabetic glucose tolerance at baseline. The prevalence of the metabolic syndrome criteria (NCEP ATP IV Criteria) were evaluated in all 4 studies. Absolute change in HbA_{1c} was evaluated in the diabetic population enrolled in RIO-Diabetes. The hierarchy of endpoints in the RIO studies is presented in Table (6.1) 1.

To ensure a global type I error rate of 5% among these endpoints, a pre-specified hierarchical testing strategy of the key secondary endpoints was implemented within each study. Tests of key secondary endpoints were performed in a sequential manner if the test of the primary endpoint was significant.

Table (6.1) 1 - Hierarchy of the endpoints in the Phase 3 RIO studies

RIO-North America	**RIO-Europe**	**RIO-Lipids**	**RIO-Diabetes**
Primary endpoint			
Body Weight at 1y Body Weight regain at 2y	Body Weight at 1 year	Body Weight at 1 year	Body Weight at 1 year
Main secondary endpoints			
HDL cholesterol Metabolic syndrome (NCEP ATP IV Criteria)	HDL cholesterol Triglycerides OGTT at 1 year Metabolic syndrome	HDL cholesterol Triglycerides OGTT Metabolic syndrome	HbA_{1c} HDL cholesterol Triglycerides Metabolic syndrome

Statistical methods

In each study, continuous endpoints were assessed as absolute changes from baseline to 1 year, with the exception of lipid measures, which were assessed as percent changes from baseline. Change from baseline at 1 year was analyzed using an analysis of variance (ANOVA) model with treatment as the fixed effect. The ANOVA model for weight also included terms for the weight loss randomization stratum (weight loss ≤2 kg or >2 kg during placebo run-in) and study specific randomization stratum, such as anti-diabetic therapy (metformin or sulfonylureas) in RIO-Diabetes and TG levels (≤4 g/L or >4 g/L at the screening visit) in RIO-Lipids. The same models were used in the pooled analyses across studies, except that a term for study was included in each model.

Categorical endpoints at 1 year in each study were analyzed using a chi-squared test; Fisher's exact test was used in the event of sparse data. 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 with 2 or 3 fixed effects, treatment and randomization strata as described in the analysis of weight change. The prevalence of metabolic syndrome was analyzed using logistic regression. A term for study was included in the logistic regression models applied to pooled data.

In the above analyses, both active treatment groups were compared with placebo using a modified Bonferroni procedure (51) to maintain the overall type 1 error rate of 5% owing to the multiplicity of doses. All statistical tests were two-sided and used a significance level of 5%.

For patients with missing endpoint values in the ITT population, the last nonmissing postbaseline value was used to calculate the change from baseline (last observation carried forward [LOCF]).

Results

The proportions of patients who discontinued treatment [Table (6.1) 2] were similar in the 3 treatment groups, the most common reason for discontinuation being "patient request." Adverse events were more frequently cited as a reason for discontinuation in the 2 active-treatment groups when compared to the placebo group. An adjudication committee has classified all patients who prematurely stopped the study drug to identify patients who might have discontinued due to AEs but were classified in other categories by the Investigators. This analysis did not change the contrast between groups [Table (7.4.1.2.3) 1].

Table (6.1) 2 - Summary of randomized patients disposition, number (%) of patients in Year 1 (RIO studies)

	RIO-North America (%)			**RIO-Europe (%)**			**RIO-Lipids (%)**			**RIO-Diabetes (%)**		
Reason for Discontinuation	**Pbo**	**5 mg**	**20 mg**	**Pbo**	**5 mg**	**20 mg**	**Pbo**	**5 mg**	**20 mg**	**Pbo**	**5 mg**	**20 mg**
N	**607**	**1216**	**1222**	**305**	**604**	**599**	**343**	**346**	**347**	**348**	**360**	**339**
Completed Year 1 treatment	50.9	51.0	55.1	58.4	62.7	60.6	62.4	60.1	63.7	66.4	64.4	67.6
Main reason for discontinuation according to Investigators												
Subject's request	22.6	21.6	17.4	24.9	20.7	17.4	20.4	20.5	12.4	12.6	15.3	8.8
Adverse event	8.1	10.0	13.8	9.2	9.1	15.4	9.3	8.4	16.1	6.0	8.3	16.2
Poor compliance to protocol	3.6	4.8	3.9	2.6	3.3	2.2	3.8	5.2	3.7	6.6	6.7	3.5
Lack of efficacy/disease progression	5.6	5.2	2.9	2.3	1.5	1.2	0.6	1.2	0.9	1.4	1.1	0.3
Subject lost to follow-up	9.2	7.0	6.5	2.6	2.3	3.3	3.5	2.9	2.3	5.2	1.4	1.2
Other reason	0	0.4	0.3	0	0.3	0	0	1.7	0.9	1.7	2.8	2.4

PGM= SR141716/OVERALL OBESITY/NDA0030/BS/PGM RPT/i dispo.sas OUT= OUTPUT/i dispo.html (27OCT2004 - 14:51)
Note: % calculated using the number of randomized subjects as denominator in each study

Patient demographics and characteristics at baseline are also shown in Table (6.1) 3. The 3 treatment groups were well matched for body weight, BMI, waist circumference, and proportions of smokers, in addition to age, gender, and race. The population included in these 4 trials was in their mid-40s with the exception of in the RIO Diabetes population, which was approximately 10 years older. Women were the majority of patients in the 2 year studies. The gender ratio was more balanced in RIO-Lipids and RIO-Diabetes studies, with men representing 40% to 50% of the patient population. Body mass index was clearly elevated across all studies with adequate representation of the morbidly obese, particularly in RIO-North America.

Elevated mean waist circumference indicated a high prevalence of abdominal obesity, with 80% to 90% of patients qualified as having abdominal obesity. The study population demographics demonstrated an overweight and obese population at increased risk of cardiovascular complications and of becoming diabetic. The most frequently reported metabolic abnormality was dyslipidemia, generally not treated pharmacologically with the exception of RIO-Diabetes, where more than 60% of the dyslipidemic patients were on a drug, generally a statin. The pre-diabetic patient with impaired fasting glucose or glucose tolerance was well represented in the program. Hypertension was frequently treated. Finally, about 45% of the population met the criteria for metabolic syndrome according to

ATP III (50). There were differences across studies for this parameter, however, with nearly 80% of enrolled patients in RIO Diabetes meeting the criteria.

Table (6.1) 3 - Characteristics at baseline - randomized and exposed patients (RIO studies)

		RIO-North America (N=3040)	RIO-Europe (N=1507)	RIO-Lipids (N=1033)	RIO-Diabetes (N=1045)
Age (years)	**N**	**3040**	**1507**	**1033**	**1045**
	Mean (SD)	45.0 (11.6)	45.0 (11.5)	47.8 (10.1)	55.6 (8.6)
Gender	Males	19.3%	20.5%	39.4%	49.1%
	Females	80.7%	79.5%	60.6%	50.9%
Race					
Caucasian		2553 (84.0 %)	1410 (93.6 %)	1000 (96.8 %)	925 (88.5 %)
Black		339 (11.2 %)	73 (4.8 %)	6 (0.6 %)	57 (5.5 %)
Asian/Oriental		12 (0.4 %)	9 (0.6 %)	3 (0.3 %)	13 (1.2 %)
Other		136 (4.5 %)	15 (1.0 %)	24 (2.3 %)	50 (4.8 %)
Weight (lbs)	**N**	**3039**	**1507**	**1033**	**1045**
	Mean (SD)	230.2 (46.9)	222.8 (43.6)	207.6 (32.7)	212.4 (32.4)
Waist (cm)	**N**	**3032**	**1504**	**1033**	**1044**
	Mean (SD)	105.8 (15.3)	108.4 (14.1)	105.0 (11.1)	109.0 (10.8)
	Males >102cm	527 (89.6 %)	289 (93.5 %)	320 (78.6 %)	416 (81.3 %)
	Females >88cm	2124 (86.9 %)	1132 (94.7 %)	571 (91.2 %)	514 (96.6 %)
BMI (kg/m2)	**N**	**3039**	**1506**	**1033**	**1045**
	Mean (SD)	37.6 (6.5)	36.0 (5.9)	33.3 (3.5)	33.7 (3.6)
	<30	152 (5.0 %)	159 (10.6 %)	194 (18.8 %)	191 (18.3 %)
	[30,35)	1100 (36.2 %)	625 (41.5 %)	500 (48.4 %)	439 (42.0 %)
	[35,40)	897 (29.5 %)	398 (26.4 %)	319 (30.9 %)	396 (37.9 %)
	>=40	890 (29.3 %)	324 (21.5 %)	20 (1.9 %)	19 (1.8 %)
Fasting glucose (mmol/L)	**N**	**3029**	**1489**	**1027**	**1024**
	Mean (SD)	5.11 (0.60)	5.28 (0.67)	5.30 (0.65)	8.30 (2.08)
	IFG [(1)]	596 (19.7%)	413 (27.7%)	281 (27.4%)	225 (22.0%)
	DFG [(2)]	32 (1.1%)	23 (1.5%)	14 (1.4%)	761 (74.3%)
Impaired Glucose Tolerance [(3)]		NA	200 (13.5%)	195 (19.0%)	NA
Diabetic Glucose Tolerance [(4)]		NA	28 (1.9%)	37 (3.6%)	NA
LDL cholesterol (mmol/L)	**N**	**3020**	**1496**	**1028**	**1024**
	Mean (SD)	3.08 (0.77)	3.18 (0.79)	3.52 (0.81)	2.99 (0.81)
	>= 3.36	1055 (34.9 %)	608 (40.6 %)	598 (58.2 %)	335 (32.7 %)
HDL cholesterol (mmol/L)	**N**	**3020**	**1495**	**1030**	**1024**
	Mean (SD)	1.26 (0.32)	1.27 (0.33)	1.10 (0.24)	1.16 (0.27)
	Males < 1.036	292 (50.3 %)	154 (50.0 %)	254 (62.6 %)	228 (45.1 %)
	Females < 1.295	1288 (52.8 %)	644 (54.3 %)	441 (70.7 %)	302 (58.3 %)
Triglycerides (mmol/L)	**N**	**3022**	**1495**	**1026**	**1022**
	Mean (SD)	1.55 (0.88)	1.45 (0.88)	2.09 (1.23)	2.00 (1.12)
	>= 1.69	1009 (33.4 %)	409 (27.4 %)	589 (57.4 %)	542 (53.0 %)
Patients with clinical criteria of Metabolic syndrome (NCEP,ATPIII)		34.9%	41.3%	53.6%	79.1%

[(1)] IFG: 5.55 mmol/L ≤ Fasting Glucose < 6.99 mmol/L, [(2)] DFG: Fasting Glucose ≥ 6.99 mmol/L, [(3)] IGT: 7.77 mmol/L <OGTT (Glucose at 120 minutes post-load) < 11.10 mmol/L, [(4)] DGT: OGTT (Glucose at 120 minutes post-load) ≥11.10mmol/L

Efficacy outcomes for weight and waist circumference

After 4 weeks on a reduced hypocaloric diet, improvements were seen in most of the efficacy outcomes measured in the 3 treatment groups [Figure (6.1) 2]. Mean weight and waist circumference decreased.

Table (6.1) 4 - Body weight (lbs) and waist circumference (cm) at 1 year - ITT population (RIO studies)

		RIO-North America		RIO-Europe		RIO-Lipids		Pooled Studies		RIO-Diabetes	
		Placebo (N=607)	20 mg (N=1219)	Placebo (N=305)	20 mg (N=599)	Placebo (N=342)	20 mg (N=346)	Placebo (N=1254)	20 mg (N=2164)	Placebo (N=348)	20 mg (N=339)
Weight (lbs)											
Baseline	N	590	1189	302	595	334	344	1226	2128	345	336
	Mean (SD)	230.8 (47.8)	227.1 (44.8)	220.3 (44.6)	224.2 (42.7)	209.5 (33.3)	205.9 (32.7)	222.4 (44.4)	222.8 (43.2)	211.6 (33.4)	210.9 (31.4)
Year 1	Mean (SD)	227.4 (49.8)	213.3 (46.3)	216.2 (46.2)	209.7 (45.3)	206.2 (35.0)	190.6 (34.0)	218.9 (46.2)	208.6 (45.0)	208.4 (33.5)	199.2 (32.0)
Change	Mean (SD)	-3.4 (12.5)	-13.8 (15.8)	-4.0 (14.0)	-14.5 (15.9)	-3.3 (11.0)	-15.3 (13.5)	-3.5 (12.5)	-14.2 (15.5)	-3.2 (7.8)	-11.7 (11.5)
	LS Mean		-10.5 (0.7)		-10.4 (1.0)		-11.9 (0.9)		-10.8 (0.5)		-8.6 (0.7)
	Difference (SE)										
	95% CI		(-11.8,-9.1)		(-12.3,-8.5)		(-13.7,-10.2)		(-11.7,-9.8)		(-10.1,-7.2)
	p versus placebo		<0.001		<0.001		<0.001		<0.001		<0.001
% Change	Mean (SD)	-1.6 (5.4)	-6.2 (6.9)	-1.8 (5.9)	-6.6 (7.2)	-1.6 (5.2)	-7.5 (6.4)	-1.6 (5.5)	-6.5 (6.9)	-1.5 (3.6)	-5.6 (5.4)
5% responder	n (%)	118 (20.0)	578 (48.6)	58 (19.2)	303 (50.9)	65 (19.5)	201 (58.4)	241 (19.7)	1082 (50.8)	50 (14.5)	166 (49.4)
	p versus placebo		<0.001		<0.001		<0.001		<0.001		<0.001
10% responder	n (%)	50 (8.5)	300 (25.2)	22 (7.3)	163 (27.4)	24 (7.2)	112 (32.6)	96 (7.8)	575 (27.0)	7 (2.0)	55 (16.4)
	p versus placebo		<0.001		<0.001		<0.001		<0.001		<0.001
Waist circumference (cm)**											
Baseline	N	585	1187	302	592	334	343	1221	2122	344	336
	Mean (SD)	105.9 (15.0)	104.9 (15.0)	107.7 (13.8)	108.7 (14.1)	105.7 (11.4)	104.7 (11.0)	106.3 (13.8)	105.9 (14.3)	109.1 (11.6)	108.6 (10.1)
Year 1	Mean (SD)	103.4 (15.5)	98.8 (15.5)	105.3 (14.3)	102.2 (15.4)	103.3 (12.6)	97.6 (12.0)	103.8 (14.5)	99.5 (15.0)	107.1 (11.5)	103.4 (10.8)
Change	Mean (SD)	-2.5 (6.9)	-6.1 (7.1)	-2.4 (6.9)	-6.5 (7.4)	-2.4 (5.7)	-7.1 (6.8)	-2.5 (6.6)	-6.4 (7.2)	-1.9 (5.5)	-5.2 (6.1)
	LS Mean		-3.6 (0.3)		-4.2 (0.5)		-4.7 (0.5)		-4.0 (0.2)		-3.3 (0.4)
	Difference (SE)										
	95% CI		(-4.3,-2.9)		(-5.1,-3.2)		(-5.7,-3.8)		(-4.5,-3.5)		(-4.2,-2.4)
	p versus placebo		<0.001		<0.001		<0.001		<0.001		<0.001

* Note: Year 1 - Last post-baseline observation in first year for RIO-North America and RIO-Europe and last post-baseline observation during study in RIO-Lipids and RIO-Diabetes. Pooled studies: RIO-Europe, RIO-Lipids and RIO-North America

** Note: Pooled studies: RIO-North America, RIO-Europe, and RIO-Lipids/ Year 1 - Last post-baseline observation in first year for RIO-North America and RIO-Europe and last post-baseline observation during study in RIO-Lipids and RIO-Diabetes

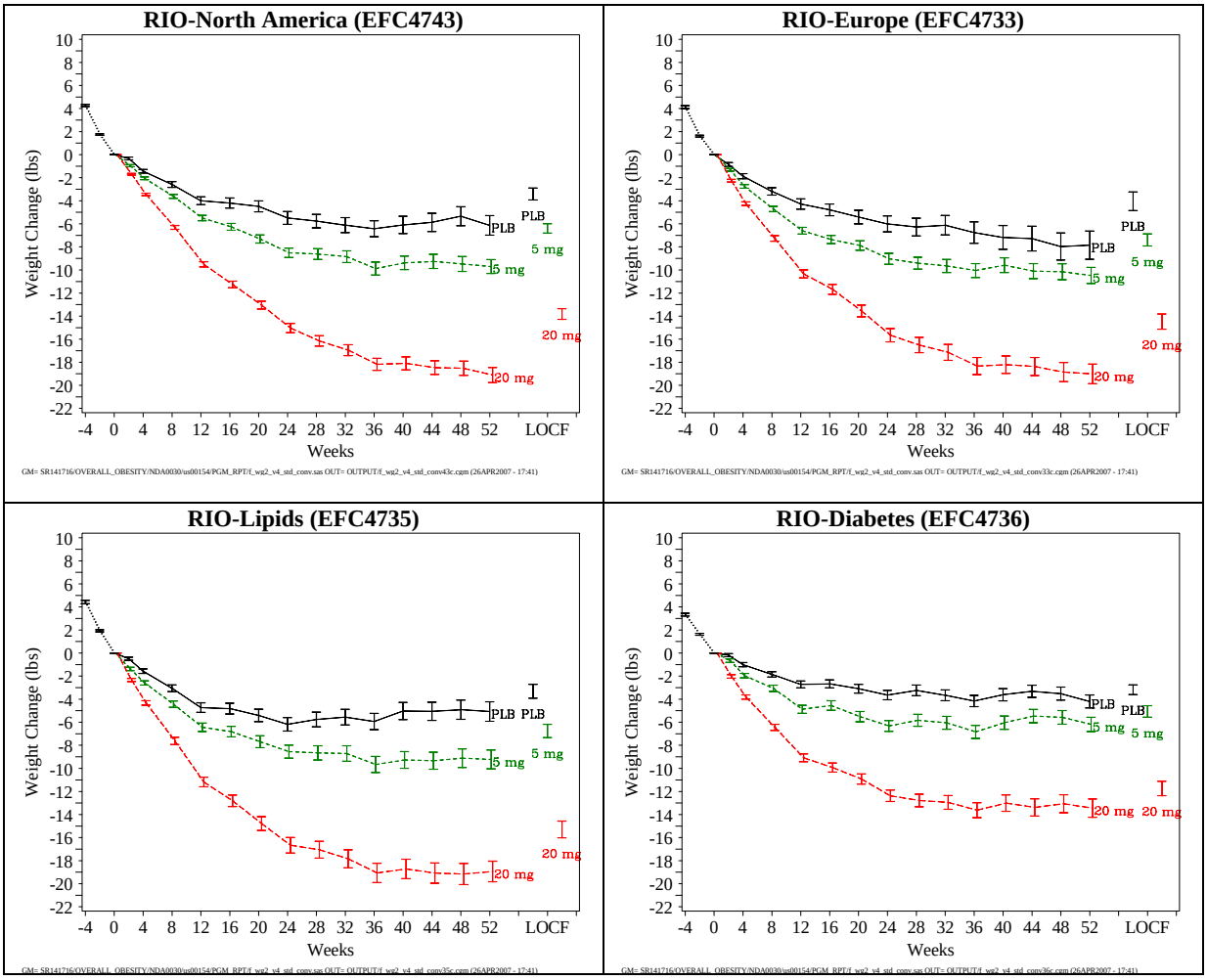

Figure (6.1) 2 - Body weight (lbs) by visit and LOCF at 1 year (mean change ± SEM) - ITT population (RIO studies)

In the 3 studies including only nondiabetic patients, body weight loss in the pooled ITT population after 1 year of treatment was greater in the rimonabant 20-mg group (14.3 lbs) when compared with the placebo group (3.5 lbs); the mean difference between the groups was statistically significant ($p<0.001$). The proportion of patients who lost at least 5% of baseline body weight was 50.8% in the rimonabant 20-mg group, but only 19.7% in patients on placebo ($p<0.001$). More than one-quarter of patients (27.0%) in the rimonabant 20-mg 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 rimonabant 20-mg (6.4 cm) than in those receiving placebo (2.5 cm; $p<0.001$). Results were remarkably consistent across studies [Table (6.1) 4].

In the RIO-Diabetes study, as expected in diabetic patients who have more difficulties in losing weight, all treatment groups lost less weight than in the nondiabetic studies; however, rimonabant 20-mg produced a significantly greater reduction in body weight ($p<0.001$) than placebo. The proportion of patients who lost at least 5% of baseline body weight was 49.4% in the rimonabant 20-mg group, but only 14.5% in the placebo group ($p<0.001$). A total of 16.4% of patients in the rimonabant 20-mg group lost at least 10% of their body weight, compared with only 2% of patients in the placebo group ($p<0.001$).

The analysis of the effect of certain demographic characteristics on the response to treatment showed significant interactions for some subgroups. Notably, significant improvements in weight loss and HDL-C were observed in both Caucasian and Black patients (see section below). There was no consistent interaction between any other demographic characteristic [eg, age, gender, BMI, and the response to rimonabant 20-mg (relative to placebo)].

Efficacy maintained at 2 years

The efficacy of rimonabant on weight was maintained at 2 years in both studies continued for that length of time, RIO-Europe and in RIO-North America. In RIO-North America, the participants who were re-randomized to placebo (N=298) regained most of their previous weight loss, as was expected in this chronic disease, while patients continuing rimonabant 20-mg (N=333) maintained their weight loss [Figure (6.1) 3].

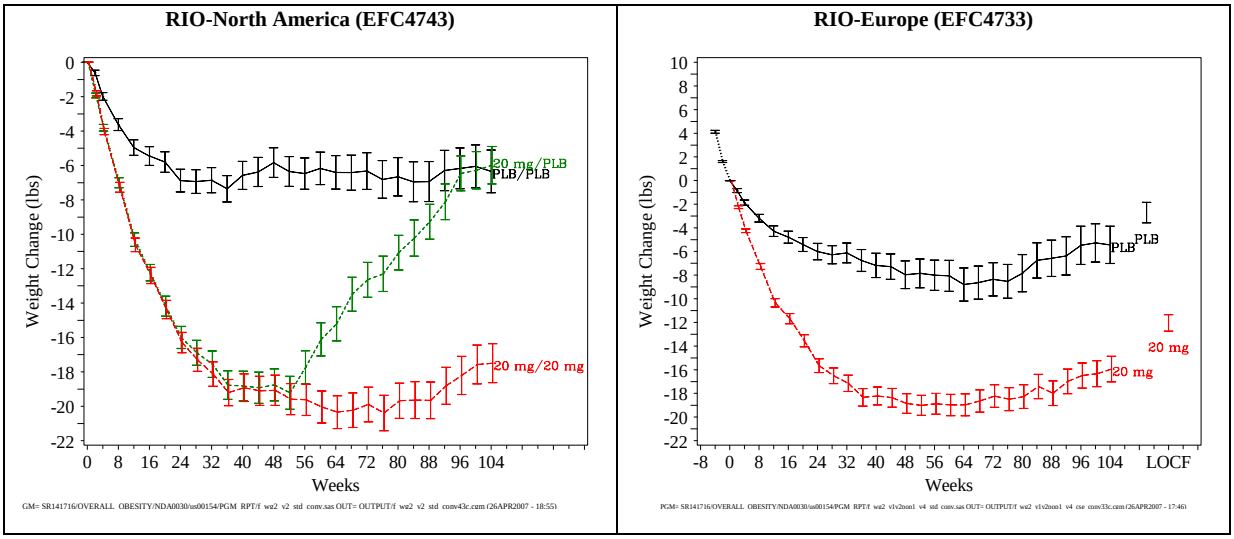

Figure (6.1) 3 - Body weight change from baseline to 2 years RIO-North America (Year 1 completers) and RIO-Europe

Morbidly obese patients
In all 4 studies, a total of 1300 patients had a BMI ≥40 kg/m^2 at screening. In this population, the efficacy of rimonabant was also demonstrated, both for weight loss (placebo subtracted difference: -5.8 kg (-12.8 lbs), p<0.001) and for metabolic improvement. In the rimonabant 20-mg group, 1 in 2 patients lost >5% of their baseline weight in the 20-mg group and 1 in 4 lost ≥10%.

In black patients the absolute difference in weight loss between rimonabant and placebo appeared smaller than in Caucasian patients, but was still significant (placebo subtracted difference -2.7 kg (-5.9 lbs), p<0.05). The interpretation of this observation should take into account the lower weight loss under placebo in black patients (only -0.5 kg [-1.1 lbs]) compared with that of the overall population (-1.6 kg [-3.5 lbs]), and also the lower exposure of these patients to rimonabant (see Section 5.2).

6.2 Type 2 diabetes mellitus

Two studies were conducted in patients with type 2 diabetes: RIO-Diabetes and SERENADE.

Over 1000 patients were randomized into the **RIO-Diabetes** study and were offered treatment for 1 year. About two-thirds were taking metformin and approximately one-third were taking a sulfonylurea, but were still not able to achieve adequate control, defined as HbA_{1c} <6.5%.

Two hundred seventy-eight drug-naive patients who had not recently been on an anti-diabetic agent were randomized into the **SERENADE** study, which was conducted for 6 months.

The populations chosen for the trials were different in terms of their background therapy, and, hence, the stage of their disease. In the RIO-Diabetes study, a type 2 diabetic population that would be most likely to receive rimonabant for glucose control was chosen, ie, one already treated with well-accepted, first-line oral anti-diabetes agents such as monotherapy. However, in the SERENADE study, a treatment-naive population was chosen to avoid the possible interference with the effects of rimonabant by any other antihyperglycemic agent, and to also compare the effectiveness, safety, and tolerability of rimonabant 20-mg in a different type 2 diabetes population than that observed in RIO-Diabetes. Despite entry criteria for age, BMI, and HbA_{1c} that differed slightly, these parameters were similar between the 2 study populations at baseline. The SERENADE study protocol pre-specified that the efficacy data obtained after either discontinuation of study double-blind treatment or the introduction of antihyperglycemic rescue medication was not analyzed.

Table (6.2) 1 provides baseline efficacy parameters in the 2 studies. Mean HbA_{1c} at screening was somewhat higher in the SERENADE study when compared to the RIO-Diabetes study, likely due to different HbA_{1c} inclusion ranges in the 2 studies (RIO-Diabetes: 6.5% to 10% and SERENADE: 7% to 10%). The mean baseline and screening HbA_{1c} values in RIO-Diabetes differed, since the baseline HbA_{1c} was obtained at randomization following a 4-week run-in period after screening, at the start of which diet and lifestyle instruction had been given.

Table (6.2) 1 - Efficacy data at baseline (RIO-Diabetes and SERENADE) - mean (SD) baseline values (randomized and exposed population)

	RIO-Diabetes		**SERENADE**	
	Placebo (n=348)	**Rimonabant 20 mg (n=339)**	**Placebo (n=140)**	**Rimonabant 20 mg (n=138)**
HbA_{1c} (%)	7.2 (0.9)	7.3 (0.8)	7.9 (0.7)	7.9 (0.8)
Body weight (lbs)	211.7 (33.3)	211.0 (31.4)	212.4 (46.1)	212.9 (46.3)
FPG (mM)	8.2 (2.2)	8.5 (2.2)	8.7 (1.9)	9.0 (1.9)
FPI (uIU/mL)	16.0 (13.3)	15.5 (11.3)	19.2 (12.3)	17.9 (14.5)
HDL-C (mM)	1.17 (0.28)	1.16 (0.26)	1.28 (0.27)	1.32 (0.34)
TG (mM)	1.93 (1.05)	2.12 (1.29)	2.17 (1.16)	2.38 (1.71)
Waist circ (cm)	109 (11.5)	109 (10.1)	109 (15.0)	109 (14.2)

Table (6.2) 2 and Figure (6.2) 1 provide the change in HbA_{1c} from baseline to study endpoint in the ITT populations in both studies and display the changes in HbA_{1c} over time in both studies, respectively. As the time for follow-up was 6 months in the SERENADE study versus 1 year for RIO-Diabetes, a vertical line is drawn on the graph for RIO-Diabetes corresponding to the 6-month visit in that study, to better compare with the SERENADE results at 6 months.

Table (6.2) 2 - Mean changes and differences from baseline in HbA_{1c} (%) at end of study* - ITT populations - RIO-Diabetes and SERENADE ITT populations (LOCF)

	RIO-Diabetes		**SERENADE**	
	Placebo	**Rimonabant 20 mg**	**Placebo**	**Rimonabant 20 mg**
N	317	315	131	130
Mean BL (SD)	7.2 (0.9)	7.3 (0.8)	7.9 (0.7)	7.9 (0.8)
Mean Δ from BL (SD)	0.1 (1.0)	– 0.6 (0.8)	– 0.3 (1.2)	– 0.8 (1.2)
LS Mean Δ versus Placebo (SE)	-	– 0.7 (0.1)		– 0.51 (0.14)
95% CI		(-0.8, -0.5)		(-0.78, -0.24)
p-value		<0.001		0.0002

*End-of-study: 1 year for RIO-Diabetes, 6 months for SERENADE

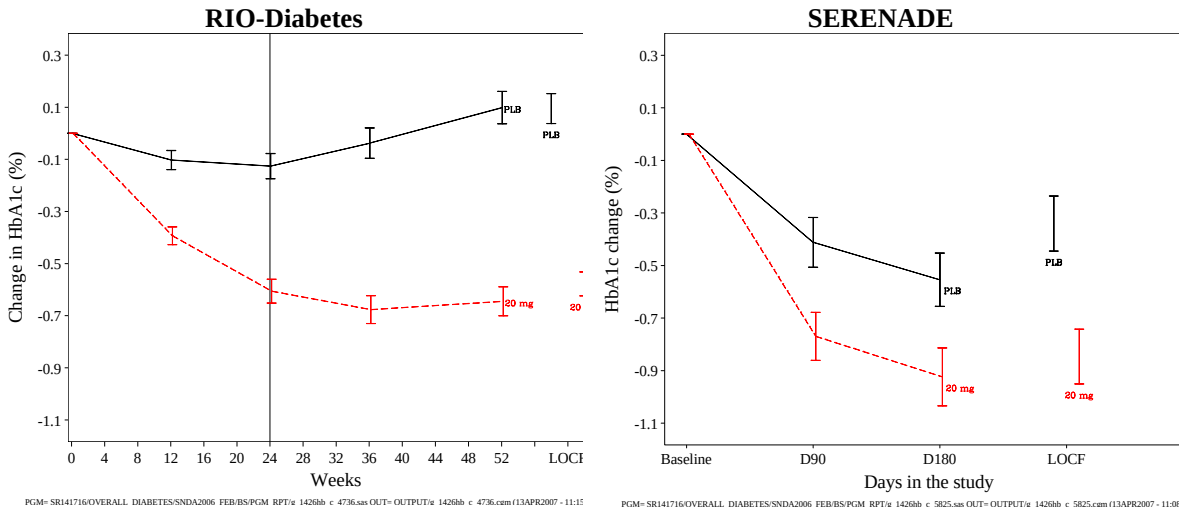

Figure (6.2) 1 - Mean change from baseline in HbA_{1c} values for RIO-Diabetes and SERENADE studies

In the SERENADE study, the placebo-subtracted change in HbA_{1c} in the rimonabant 20-mg group at the end-of-study analysis of -0.51% was very close to the -0.5% placebo-subtracted treatment effect in the rimonabant 20-mg group in the RIO-Diabetes study at 6 months. The curves for the rimonabant 20-mg group at 6 months showed no evidence for a plateau in HbA_{1c} in the SERENADE study and the mean HbA_{1c} was continuing to fall in the RIO-Diabetes study Figure (6.2) 1. Notably, the placebo curve appeared to reach a nadir at 6 months and an increase in mean HbA_{1c} in the placebo group over the subsequent 6 months to levels greater than baseline was observed. A nadir in the rimonabant 20-mg HbA_{1c} curve in the RIO-Diabetes study was reached only at 9 months, and the 9-month mean HbA_{1c} was maintained thereafter over the last 3 months of follow-up.

In the RIO-Diabetes study, patients were stratified according to their oral anti-diabetic medication. Approximately two-thirds of patients were on a stable dose of metformin and one-third of patients were on a stable dose of sulfonylurea. These groups were large and could have been studied in 2 different studies. The RIO-Diabetes study evaluated the 2 populations under the same trial conditions. There was a comparable improvement in HbA_{1c} in the rimonabant 20-mg groups, with both showing a highly significant -0.7 point reduction. The percentage of patients who achieved adequate glucose control (HbA_{1c} <7%) was significantly greater in the rimonabant 20-mg group compared with the placebo group [Table (6.2) 3].

Table (6.2) 3 - Percent of patients with HbA_{1c} <7% at end of study - ITT population

	N	Placebo	N	Rimonabant 20 mg	p
Percent of patients with HbA_{1c} <7%					
Rio-Diabetes	317	47.6%	315	67.9%	<0.001
SERENADE	131	35.1%	130	50.8%	0.0122
Percent of patients with HbA_{1c} <6.5%					
Rio-Diabetes	317	20.8%	315	42.9%	<0.001
SERENADE	131	16%	130	23.8%	0.09

Weight loss in the RIO-Diabetes and SERENADE studies were comparable [Table (6.2) 4].

Table (6.2) 4 - Mean changes and differences from baseline in body weight (lbs) at end of study - ITT populations - RIO-Diabetes and SERENADE

	RIO-Diabetes		SERENADE	
	Placebo	Rimonabant 20 mg	Placebo	Rimonabant 20 mg
N	345	336	138	135
Mean baseline (SD)	211.6 (33.4)	210.9 (31.4)	211.8 (46.2	213.0 (46.5)
Mean Δ from BL (SD)	-3.2 (7.8)	-11.7 (11.5)	-6.2 (10.6	-14.7 (12.2)
LS Mean Δ versus placebo (SE)		-8.6 (0.7)		-8.46 (1.34)
95% CI		(–10.1, –7.2)		(–11.09, –5.83)
p-value		< 0.001		< 0.0001

6.3 Other Cardiometabolic factors

Dyslipidemias

Patients who received rimonabant also showed statistically significant improvements compared with placebo in lipid parameters. The increase from baseline in HDL-C and the reductions in TG, and the total cholesterol:HDL-C ratio were markedly greater in patients receiving rimonabant 20-mg when compared to those receiving placebo ($p<0.001$). Non HDL-C, the atherogenic fraction of lipoproteins, slightly decreased. Overall, low-density lipoprotein-cholesterol (LDL-C) levels remained unchanged. Very consistent results were observed in the 4 RIO studies [Figure (6.3) 1].

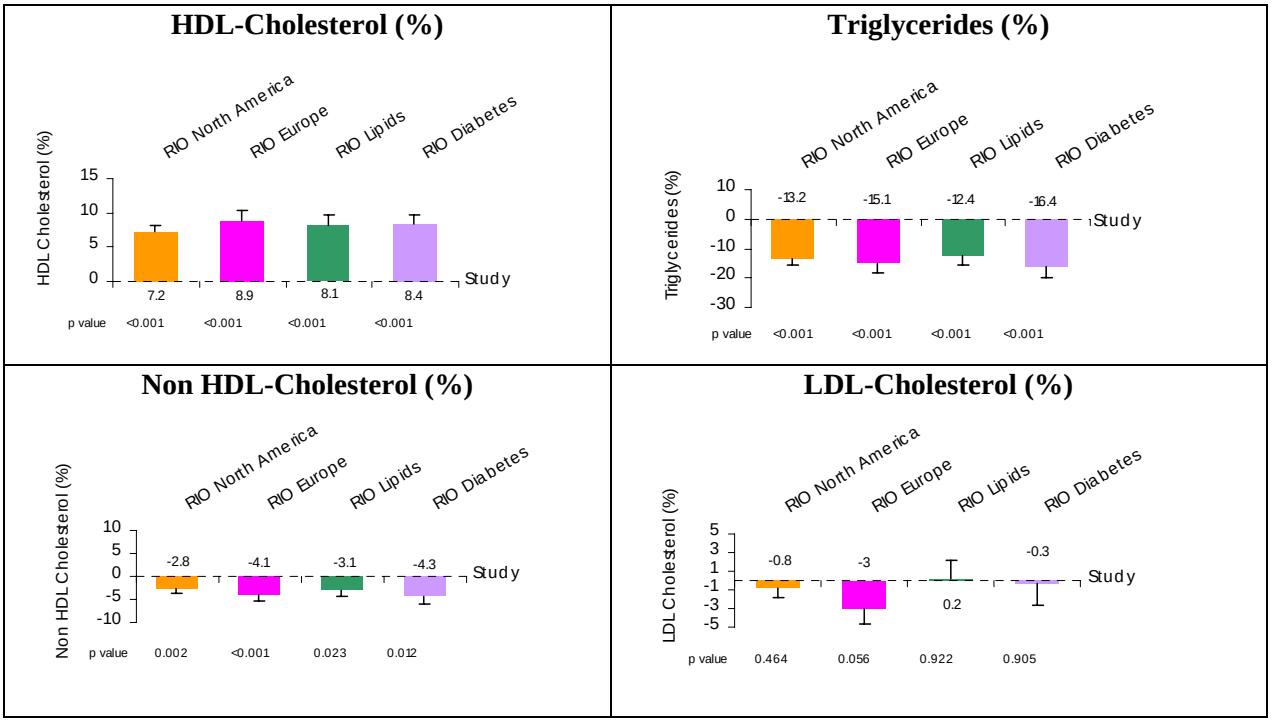

Figure (6.3) 1 - Serum lipids and lipoproteins in the 4 pivotal clinical trials - mean percent changes (SE) relative to the change in the placebo group

Patients in the RIO-Lipids study were not taking a drug for dyslipidemia. In contrast, most patients in the RIO-Diabetes study were taking a drug for dyslipidemia, generally a statin. Comparable improvements in HDL-C and TG were seen in these 2 study populations [Figure (6.3) 2 and Figure (6.3) 3].

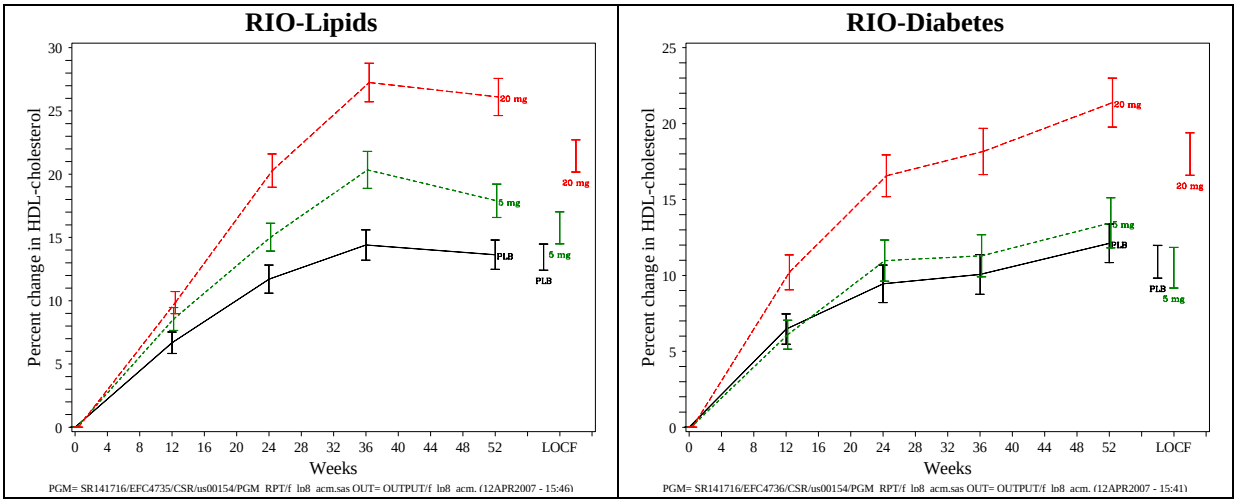

Figure (6.3) 2 - HDL-C (mean percent change ± SEM) by visit and at 1 year (LOCF) - ITT population - patients with low HDL-C at baseline

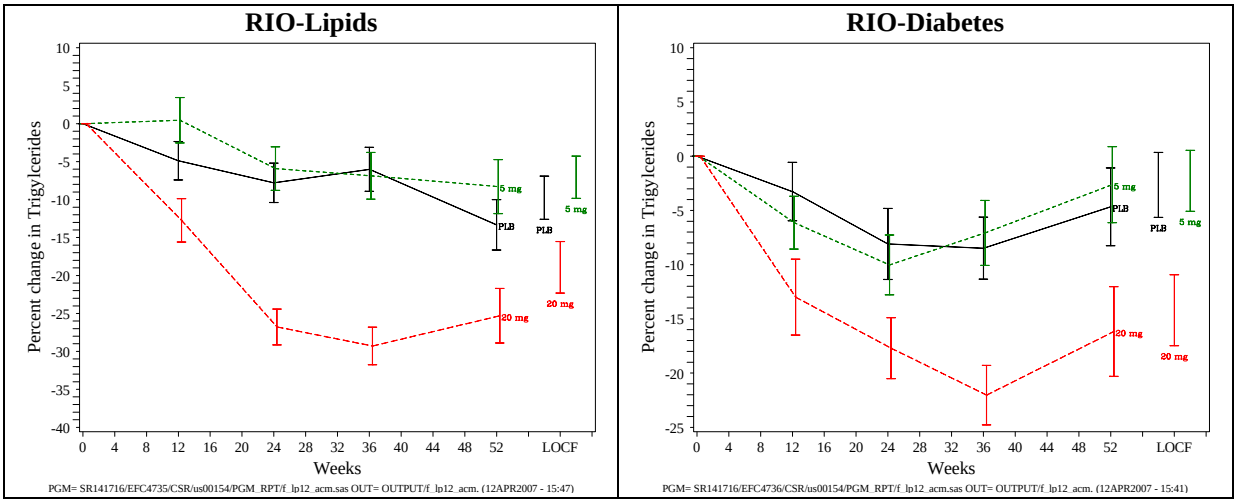

Figure (6.3) 3 - TG (mean percent change ± SEM) by visit and at 1 year (LOCF) - ITT population - patients with hypertriglyceridemia at baseline

There was no difference in change in total cholesterol and in LDL-C between groups. The LDL particle size, an indicator of the atherogenicity of the LDL particles, was measured using the PAGGE method (as an exploratory evaluation). In the rimonabant 20-mg group, there was a reduction in the relative proportion of small LDL particle sizes (the atherogenic particles) of -4.7 ± 1.5%, [-7.7, -1.7], p=0.002, and an increase in relative proportion of large LDL compared with the placebo group of 6.3 ± 1.6%, [3.1, 9.4], p<0.001.

In the RIO-Europe [Figure (6.3) 4] and RIO-North America studies, patients treated for 2 years maintained their improvement in HDL-C and TG.

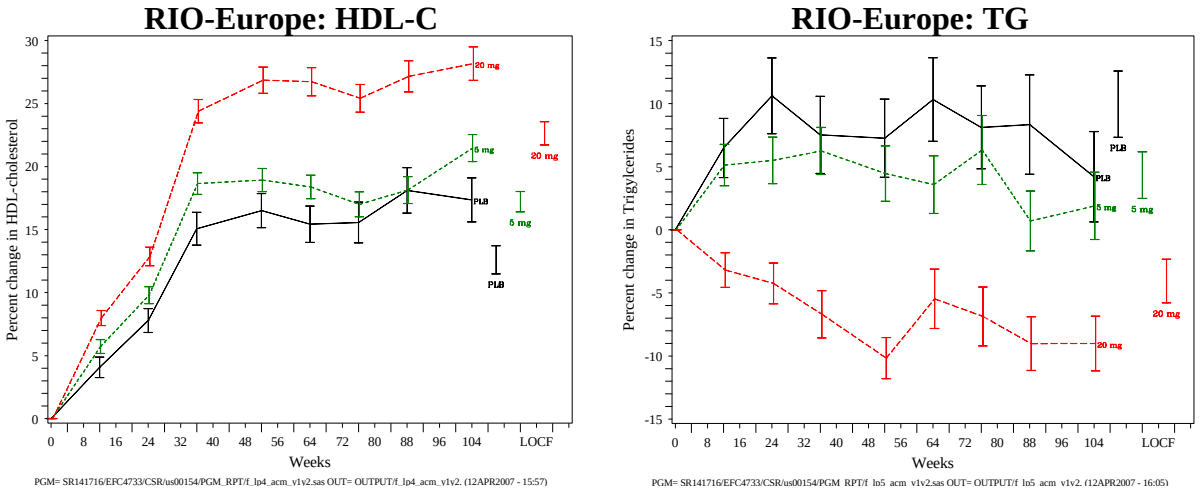

Figure (6.3) 4 - RIO-Europe - HDL-C and TG (mean percent change ± SEM) by visit and LOCF at 1 and 2 years - ITT population

Other results

Metabolic syndrome

At 1 year, the prevalence of metabolic syndrome in the rimonabant 20-mg group was reduced to a much greater degree than in the placebo group [Table (6.3) 1].

Table (6.3) 1 - Number (%) of patients with metabolic syndrome (NCEP-ATPIII definition) at 1 year - ITT population (RIO studies)

		RIO-North America		**RIO-Europe**		**RIO-Lipids**		**RIO-Diabetes**	
		Placebo (N=607)	**20 mg (N=1219)**	**Placebo (N=305)**	**20 mg (N=599)**	**Placebo (N=342)**	**20 mg (N=346)**	**Placebo (N=348)**	**20 mg (N=339)**
Metabolic syndrome (ATP III)									
Baseline	N	530	1081	271	540	310	314	316	318
	n (%)	168 (31.7)	376 (34.8)	108 (39.9)	228 (42.2)	161 (51.9)	166 (52.9)	251 (79.4)	252 (79.2)
Year 1	n (%)	155 (29.2)	229 (21.2)	85 (31.4)	106 (19.6)	127 (41.0)	81 (25.8)	232 (73.4)	204 (64.2)
	Odds ratio		0.541		0.440		0.429		0.597
	95% C.I.		(0.415,0.706)		(0.303,0.638)		(0.295,0.623)		(0.412,0.866)
	p versus placebo		<0.001		<0.001		<0.001		0.007

Note: Year 1 - Last postbaseline observation in first year for RIO-North America and RIO-Europe and last postbaseline observation during study in RIO-Lipids and RIO-Diabetes

Prediabetics

In the 3 nondiabetic studies, 1359 prediabetic patients defined as having fasting glucose ≥5.55 mmol/L and <6.99 mmol/L were included. In this population at increased risk of diabetes, significant improvements following rimonabant 20-mg per day for 1 year compared with placebo were observed in fasting insulin levels and insulin resistance as expressed by HOMA estimation [Table (6.3) 2].

Table (6.3) 2 - Population of prediabetic patients in the RIO studies

	Placebo (N=305)	**Rimonabant 20 mg (N=535)**	**Placebo (N=305)**	**Rimonabant 20 mg (N=535)**	**Placebo (N=305)**	**Rimonabant 20 mg (N=535)**
	FASTING INSULIN		**FASTING GLUCOSE**		**HOMA-IR**	
Baseline						
N	279	487	281	493	279	487
Mean (SD)	16.5 (12.8)	16.3 (146)	6.02 (0.53)	6.03 (0.52)	4.45 (3.64)	4.45 (4.35)
Year 1						
Mean (SD)	17.3 (20.5)	13.3 (9.4)	5.80 (0.85)	5.72 (0.95)	4.74 (8.04)	3.46 (2.85)
Change						
Mean (SD)	0.8 (18.4)	-3.0 (14.0)	-0.22 (0.91)	-0.31 (0.95)	0.28 (7.36)	-0.99 (4.39)
LS Mean		-3.8 (1.2)		-0.10 (0.06)		-1.26 (0.44)
Difference (SE) 95% CI		(-6.1, 1.4)		(-0.22, 0.03)		(-2.12, 0.39)
p versus placebo		0.002		0.138		0.004

Adiponectin

In the RIO-Lipids study, there was a 46% increase in plasma adiponectin levels among patients who received rimonabant 20-mg for 1 year; such an increase being greater than the increase noted in the placebo group ($p<0.001$) [Table (6.3) 3]. Regression analysis revealed that 52% of the increase in adiponectin levels was independent of body weight loss [Table (6.3) 2]. These results were confirmed in the SERENADE study in type 2 diabetic patients with an increase in adiponectin of 25%. Approximately 67% of the change in adiponectin was independent of weight loss.

Table (6.3) 3 - Mean change from baseline in adiponectin parameters at 1 year (LOCF) - ITT population - RIO-lipids

	Placebo			**Rimonabant**					
				5 mg			**20 mg**		
	N	**Mean (SD)**		**N**	**Mean (SD)**		**N**	**Mean (SD)**	
Adiponectin (mcg/mL)									
Baseline	231	5.7	(2.5)	222	5.8	(2.9)	238	5.9	(2.9)
Year 1	231	6.4	(2.9)	222	6.8	(3.5)	238	8.1	(3.8)
Change	231	0.7	(1.9)	222	1.0	(2.0)	238	2.2	(2.5)
Percent change	231	16.7	(38.7)	222	22.3	(38.0)	238	46.2	(57.8)

Patients given rimonabant 5-mg showed superiority over placebo for several efficacy variables, but responses to this dosage were consistently less pronounced than in the 20-mg group.

6.4 Weight-independent effects in the RIO studies

Randomized trials properly assess treatment effect and any such effect observed is causally a result of treatment and treatment only. Therefore, the observed metabolic effects found in the RIO studies are a direct causal result of rimonabant treatment, whatever the mechanism(s) of action.

Because both weight loss and any metabolic effects are measured postrandomization (treatment), empirical correlations between weight and metabolic effect can be established at baseline (pooling all groups) and postrandomization (by treatment group), and between changes in weight and changes in metabolic postrandomization (by treatment group). One can expect that treatment may affect the correlation between these effects.

Although it is not possible to partition definitively the treatment effect on metabolic parameters into those causally attributable to weight loss and those not attributable to weight loss, one could, however, through proper analysis models, try to quantify empirically the amount of treatment effect that is associated with weight loss, even though, this empirical estimate is not necessarily a causal effect of weight loss. Accordingly, a prespecified regression analysis was performed in order to provide some quantitative assessment of the degree to which the observed effects might be mediated by direct effects not attributed to body weight loss.

6.4.1 Effect of rimonabant on body weight and metabolic changes using regression methodology

All analyses of weight-loss independence presume some underlying effect of body weight loss on metabolic parameters, so that an assessment of the direct effect of rimonabant must therefore, remove the portion of the effect that is associated with (and possibly due to) body weight change. This relationship is deduced from the metabolic effects of body weight loss in the placebo group.

For lipid parameters, the prespecified analysis was performed on the pooled ITT LOCF data from the first year of the 4 RIO studies. For glycemic control parameters, the analysis of HbA_{1c} in diabetic patients was based on RIO-Diabetes and the analysis of fasting insulin was based on pooled data from the 3 studies in nondiabetic patients (RIO-North America, RIO-Europe, and RIO-Lipids), since improved glycemic control in diabetic patients would confound the fasting insulin measurements.

Results are for the LOCF analysis of the ITT population, unless otherwise stated.

Methods

The primary analysis of the direct effect of rimonabant, as described in the statistical analysis plan, was based on a standard regression methodology in which the body weight loss is introduced as a postrandomization covariate [analysis of covariance (ANCOVA)]. The formal statistical model is as follows:

$$Y = \alpha + \beta T + \gamma W + \varepsilon$$

where Y is the metabolic response parameter, T is the treatment indicator, and W is the body weight loss. Note that all models used in this section and the later ones also included a study term if they contained data from multiple studies. In this analysis, β is the adjusted treatment effect of rimonabant, independent of body weight loss.

This compares to the overall (unadjusted) treatment effect of rimonabant β_1 determined from the model:

$Y = \alpha + \beta_1 T + \varepsilon_1$ the proportion of the effect not explained by body weight as calculated by β/β_1.

An interaction term between body weight loss and treatment was also added to the model and assessed. This term, if significant ($p<0.05$), is indicative of a difference in the regression sloped between treatment groups and would, thereby, indicate weight-independent treatment effect. The results of this analysis are also reported.

Results

The results of the Sponsor's prespecified regression analyses are shown in Table (6.4.1) 1. After adjustment for body weight loss, rimonabant 20-mg had a clear effect in increasing HDL-C and adiponectin and in reducing TG. Body weight-independent decreases were also seen for HbA_{1c} in diabetic patients and for fasting insulin in nondiabetic patients. These results suggested that approximately 50% of the overall treatment difference is associated with (and presumably possibly attributable to) body weight change, whereas the remaining approximately 50% of the effect was not associated with (and presumably not attributable to) body weight change.

Table (6.4.1) 1 - Summary of results for primary analysis of metabolic parameters with and without adjustment for body weight loss, mean (SEM)

Parameter	Overall Treatment Effect β_1	Effect independent of Weight Loss β	% of overall effect not explained by weight β/β_1
HDL-C (%)	8.0 (0.6) p<0.001	3.6 (0.6) p<0.001	45%
TG (%)	-14.0 (1.4) p<0.001	-6.5 (1.4) p<0.001	46%
HbA_{1c} (%)	-0.67 (0.07) p<0.001	-0.37 (0.07) p<0.001	55%
Fasting insulin (µIU/mL)	-2.74 (0.48) p<0.001	-1.34 (0.51) p = 0.018	49%
Adiponectin (µg/mL)	1.5 (0.2) p<0.001	0.85 (.21) p<0.001	57%

HbA_{1c} = RIO-Diabetes
Fasting glucose/insulin = RIO-North America, RIO-Europe and RIO-Lipids

Significant interactions were found between treatment and body weight loss for HDL-C ($p<0.001$) and HbA_{1c} ($p<0.001$). This indicates that the relationship between these parameters varied differently with body weight loss among treatment groups, eg, that the statistical relationship between the change in HDL-C (and also HbA_{1c}) and the change in body weight varied differently with respect to body weight among the different treatment groups, providing further evidence for a weight-loss independent effect.

6.4.2 Categorical analysis

Results for HDL-C and HbA_{1c} are illustrated in the following histograms. Note that when looking at the metabolic parameters in the different weight loss categories, a consistent increase in HDL-C was observed for rimonabant versus placebo in all categories of patients who had similar weight loss. In diabetic patients, HbA_{1c} decreased in rimonabant patients relative to placebo in all weight loss categories except in those patients losing more than 10 kg (22 lbs) (it should be noted that there were few such patients in the placebo group in this weight change category) [Figure (6.4.2) 1].

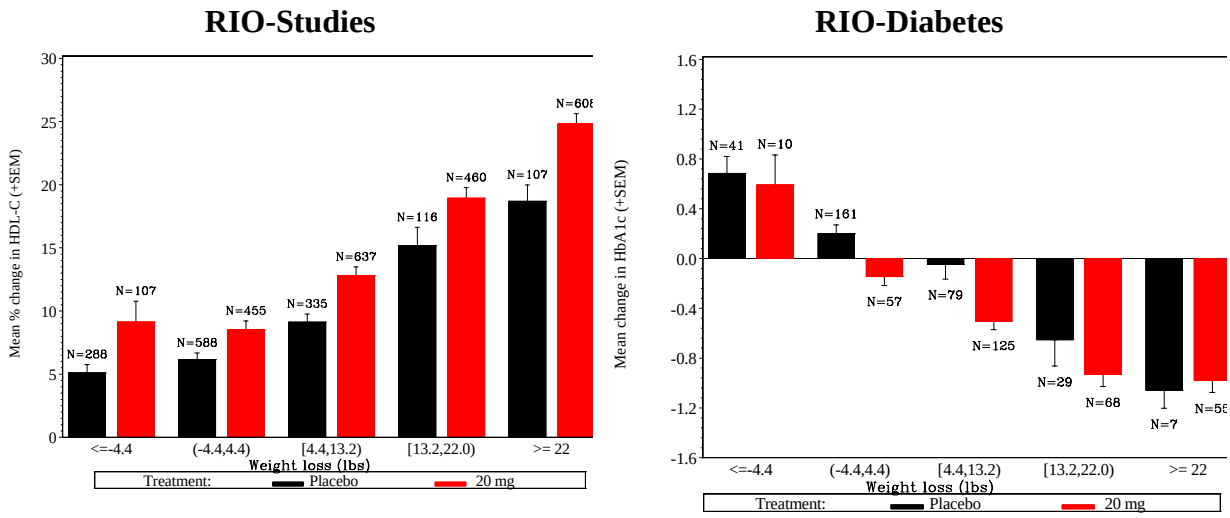

Figure (6.4.2) 1 - Relationship between weight loss and HDL-C at 1 year (ITT population - all 4 RIO studies) and Relationship between weight loss and HbA_{1c} at 1 year - ITT population (RIO-Diabetes)

The Sponsor had prespecified the regression model approach as the primary analytical tool to explore the relationship between body weight and the prespecified metabolic parameters (provided that these parameters exhibited significant treatment effects overall). In order to provide further support for any results from these analyses that assess weight-independent effects, an external statistical panel was convened and consulted to identify alternative complimentary statistical analyses that would reinforce the results of the prespecified regression analysis. Additionally, it should be emphasized that the external consultants remained blinded to the clinical results of the Phase 3 rimonabant studies, although they were provided with aggregate data pooled across all treatment groups, in order to better formulate their statistical recommendations. All direct contacts between the Sponsor and the consultants were conducted by a company employee who was not involved in the rimonabant Phase 3 development program and who was also blinded to the study results. The results of the analysis, although not presented here, were similar to, and confirmed the Sponsor's analysis.

6.5 Summary of analyses and conclusions

In the treatment of obesity, the efficacy of rimonabant 20-mg used in conjunction with a reduced calorie diet and physical exercise was demonstrated in 4 adequate and well-controlled studies with reproducible results, and sustained over time, up to 1 year in all 4 studies, and up to 2 years in 2 studies. The 5-mg dose had a modest effect on metabolic parameters in spite of its effect on body weight loss. In contrast, rimonabant 20-mg had obvious and favorable metabolic effects including increased HDL-C and decreased TG, above and beyond its significant effect on body weight loss.

In the treatment of diabetes, 2 studies demonstrated that rimonabant 20-mg significantly improved glucose control and decreased body weight, with the same improvements in dyslipidemia associated with type 2 diabetes as in nondiabetic patients.

The mode of action of rimonabant combines both central and peripheral effects. Rimonabant acts on the central regulation of food intake, helping patients to cope with the reduced caloric diet. It also acts by blocking the CB_1 receptors on the adipocytes, as shown by the increased adiponectin levels, beyond the effect on body weight loss. This dual mode of action likely explains the observed improvement in insulin sensitivity, glucose control, and lipid profile beyond that expected from the observed body weight loss.

7. SAFETY

7.1 Sources of information

A total of 59 clinical studies were completed as of 01 March 2007, involving over 16 000 subjects, of whom 15 034 were exposed to at least 1 dose of rimonabant, as follows:

- 1190 healthy subjects were enrolled in 40 Phase 1 studies during which they received single (1-mg up to 300-mg) or multiple (1-mg up to 80-mg daily for 6 days up to 4 weeks) doses of rimonabant;
- 1008 patients were enrolled in 6 Phase 2 studies conducted in various indications, (obesity, smoking cessation, alcoholism, schizophrenia), where they received multiple doses of rimonabant 5-, 10-, 20-, or 40-mg daily from 6 up to 24 weeks [Table (7.1) 1].

Table (7.1) 1 - Number of patients in the Phase 2 studies

			Rimonabant				
Study Name	**Placebo**	**Haloperidol**	**5 mg**	**10 mg**	**20 mg**	**40 mg**	**All doses**
Obese Patients							
PDY3796	22	-	-	-	-	23	**23**
DRI3388	73	-	67	68	69	-	**204**
DRI5747	131	-	133	130	132	-	**395**
Smokers Patients							
ACT4389	183	-	-	-	-	183	**183**
Others							
ACT4855 (ACTOL in alcohol dependence)	127	-	-	-	131	-	**131**
METATRIAL (Schizophrenia)	98	98	-	-	72	-	**72**
TOTAL	*634*	*98*	*200*	*198*	*404*	*206*	*1008*

- 12 836 patients were enrolled in 13 Phase 3 studies conducted in 3 different settings [Table (1.7) 1]:
  - 5262 obese patients allocated to rimonabant 5-mg (N=2520) or 20-mg (N=2742) daily for up to 2 years (see respective designs of the 7 obesity studies in Section 6.1);
  - 835 patients with type 2 diabetes allocated to rimonabant 5-mg (N=358) or 20-mg (N=477) for up to 1 year, of whom 697 were obese and counted in the above obese population (see respective designs of the type 2 diabetes studies in Section 6.2);
  - 7436 smokers willing to quit allocated to rimonabant 5-mg (N=2869) or 20-mg (N=4567) during:
- 3 placebo-controlled short-term studies of 10-week duration, where 1308 patients were exposed to rimonabant (518 to 5-mg and 790 to 20-mg);
- STRATUS-WW study, involving 5374 patients in a non-placebo-controlled 10-week period (5-mg in 2351 patients and 20-mg in 3023 patients) followed by a 1 year placebo-controlled study;
- CIRRUS 9-week non-placebo controlled study (13 weeks including follow-up) where all the 754 patients received rimonabant 20-mg daily on top of NRT or placebo.

In addition to this development program, there were 11 ongoing studies as of 01 March 2007, including 3 Phase 1 studies and 8 clinical trials involving 14 280 patients [blinded treatment (rimonabant 20-mg or placebo with randomization ratio 1:1)].

Table (7.1) 2 - Ongoing Phase 1 studies with randomized patients as of 01 March 2007

Phase – Study number (name) **Study title**	**Number of subjects/patients exposed as of 01 March 2007**
Phase 1 – PDY5352 Clinical trial of the cannabinoid CB_1 receptor antagonist, SR141716 (rimonabant) 20-mg to reduce voluntary ethanol drinking in healthy, non-treatment seeking individuals who consume between 20 and 50 drinks per week	44
Phase 1 – PDY6632 A randomized, double-blind, two-arm, placebo-controlled, parallel group study of effect of repeated oral 20-mg dose of rimonabant for 21 days on endocannabinoid release in adipose tissue of healthy male or female, lean and obese subjects	31
Phase 1 – POP10059 An open-label, single dose study of pharmacokinetic and pharmacodynamic of rimonabant 20-mg in male and female subjects with renal impairment versus subjects with normal renal function	5

Table (7.1) 3 - Ongoing Phase 3 studies with randomized patients as of 01 March 2007

Phase – Study number (name) **Study title**	**Number of subjects/patients exposed as of 01 March 2007 (Patient years)**
Phase 3B – EFC5823 (ADAGIO-Lipids) A randomized, double-blind, two-arm, placebo-controlled, parallel-group, multicenter study of rimonabant 20-mg OD in the treatment of atherogenic dyslipidemia in abdominally obese patients.	799 (682)
Phase 3B – EFC5826 (CRESCENDO) Randomized, multinational, multicenter, double-blind, placebo-controlled, two-arm, parallel-group trial of rimonabant 20-mg OD for reducing the risk of major cardiovascular events in abdominally obese patients with clustering risk factors.	8269 (3671)
Phase 3B – EFC5827 (STRADIVARIUS) Randomized, multicenter, double-blind, placebo-controlled, two-arm parallel-group trial of rimonabant 20-mg OD, for inhibition of atherosclerosis progression assessed by IVUS (intravascular ultrasounds), in overweight patients with clustering risk factors.	838 (1070)
Phase 3B – EFC5828 (AUDITOR) Randomized, multicenter, double-blind, placebo-controlled, two-arm, parallel-group trial of rimonabant 20-mg OD, for inhibition of atherosclerosis progression assessed by carotid artery intima-media thickness (CIMT), in overweight patients with additional risk factors.	660 (654)
Phase 3B – PMC0172 (VICTORIA) A randomized, double-blind, two-arm placebo controlled, 12-month study of the effects of rimonabant 20-mg once daily on the amount and the activity of visceral fat in abdominally obese patients with metabolic syndrome.	229 (115)
Phase 3B – EFC5593 (ARPEGGIO) A multicenter, randomized, placebo-controlled, double-blind, parallel-group, fixed-dose study evaluating the effect of one dose of rimonabant (20-mg/day) on glycemic control in type 2 diabetic patients inadequately controlled with insulin.	366 (245)
Phase 3B – EFC5107 (RAPSODI) A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy and safety of long-term administration of rimonabant in the prevention of Type 2 diabetes in patients with prediabetic status (ie, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both)	2397 (1005)
Phase 3B – EFC6001 (RIO ASIA) A randomized, double-blind, placebo-controlled, parallel-group, fixed-dose (rimonabant 20-mg), multi-national, multicentre study of weight-reducing effect and safety of rimonabant in obese patients with or without comorbidities.	642 (413)
Total	14 200 (7855)

OD = once daily

7.2 Collection of safety data

In all clinical studies, safety data were collected at scheduled visits by the reporting of AEs and the monitoring of laboratory values, vital signs, and ECGs.

All AEs, whether serious[1] or not, were collected by open-ended questioning from the time that the patient gave his/her consent up to the end-of-study visit. Treatment-emergent adverse events (TEAEs) were defined as AEs that occurred during double-blind study treatment exposure or within 5 half-lives (75 days) following the last double-blind investigational product intake. In the RIO studies, no off-drug follow-up period was performed. In the STRATUS studies (with the exception of EFC5794), there was a 6-week follow-up period after the last drug intake during which all AEs were collected; subsequently, for the rest of the 48-weeks follow-up period, only SAEs were collected.

During the conduct of the studies, affective symptoms were more intensively monitored using the Hospital Anxiety and Depression (HAD) self-assessment scale (52),(53).

As mentioned in the regulatory background (Section 1), following the FDA Action Letter and upon agreement with the FDA, 3 processes were instituted to clarify and supplement data on the rimonabant safety profile, and concurrence on all the methods used in these processes was obtained from and agreed upon by the Agency:

- The first process, to ensure consistency across studies, was to recode into MedDRA Version 9.0 the AEs from all completed Phase 2 and 3 studies and AEs from relevant Phase 1 studies;
- The second process was to retrospectively obtain and capture in a new database additional information on AEs of relevant interest that occurred in the completed studies: psychiatric events (particularly depression-related events, and suicidality-related events), neurological events (including sensory changes, motor impairments, cognitive difficulties and seizures), and events relevant for abuse liability assessment. Additional data collection for these events was also prospectively performed in ongoing clinical studies;
- The third process established an independent Adjudication Committee to review and reclassify all the reasons for discontinuation for individual patients who discontinued prematurely (by convention, those who dropped out for AEs remained classified in the same “AE” category). This committee classified the reasons blinded to the treatment assignments.

[1] ICH Seriousness criteria: death; life-threatening; involves or prolongs in-patient hospitalization; involves persistence or significant disability; other medically important event

7.3 Methods of analysis of safety data

All methods of analysis of safety parameters are based on recommendations from the Common Technical Document guidance (54).

In accordance with these guidelines, the safety tables are presented combining data from each individual program:

- The obesity program combined data from the 7 Phase 3 studies conducted in this indication;
- The type 2 diabetes program combined data from the 2 studies carried out in this indication, of which 1 study was already taken into account in the above obesity pooling;
- The smoking cessation program included data from the 5 studies conducted in this indication;
- In addition, a global pooling of data from the 2 main programs (obesity and smoking cessation) was done to facilitate a more global assessment of the safety profile of rimonabant in treated patients.

Given the re-randomization component of 2 large studies (Section 6.1) for the accounting of the 8414 patients (RIO-North America and STRATUS-WW), the re-randomized patients were counted twice, once in their initial treatment group and once in their re-randomized treatment groups [Figure (7.3) 1], ie:

- 626 patients from the RIO-North America study were counted in their original treatment group (ie, 300 patients in the rimonabant 5-mg group and 326 patients in the rimonabant 20-mg group); and all 626 patients were counted in the placebo group following re-randomization;
- 999 patients from the STRATUS-WW study were counted in their original treatment group (ie, 322 patients in the rimonabant 5-mg group and 677 patients in the rimonabant 20-mg group), and they were also counted either in the placebo group (ie, 664 patients) or in the rimonabant 5-mg group (335 patients) following the treatment reallocation.

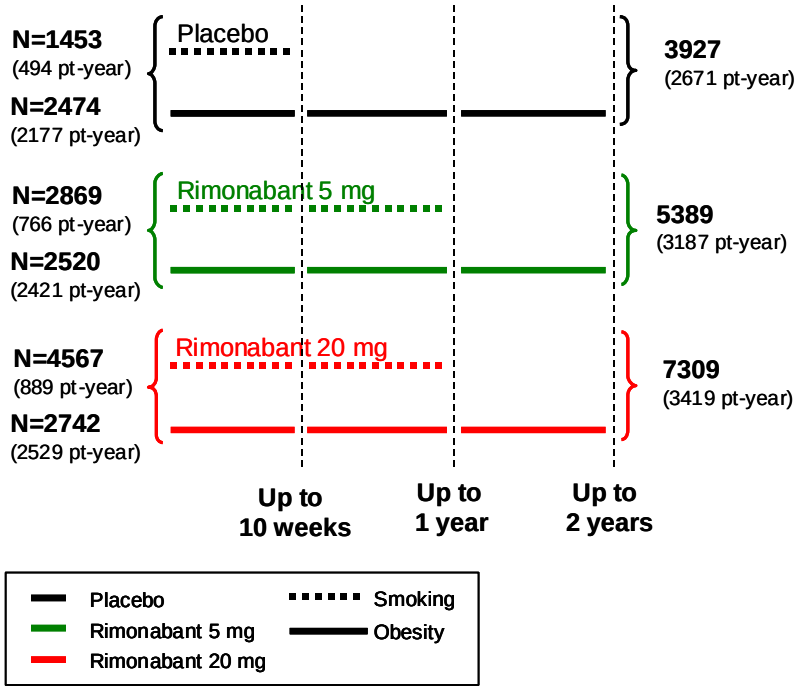

Figure (7.3) 1 - Safety population involving patients exposed to the same treatment throughout entire participation

For each studied population, treatment-emergent adverse events (TEAEs, defined as events occurring during treatment up to 75 days postdosing) were analyzed and the safety tables present the number and frequency of patients with at least 1 TEAE in each category of SOC, High-Level Group Term (HLGT), High-Level Term (HLT), or Preferred Term (PT), following the predefined MedDRA hierarchy. Most common TEAEs were defined as those reported in at least 2% frequency in any treatment group. Specific methods were used for the analysis of SAEs (including deaths) or seizures (eg, incidence rates computed using a denominator of patient-years); or analysis of suicidality-related events (eg, methodology developed by Dr Kelly Posner at Columbia University Suicidality Research Group). Outlines of these methods will be given in the corresponding sections dedicated to AEs of interest (Section 7.5).

7.4 Overall safety profile

7.4.1 Safety from completed studies

7.4.1.1 Phase 1 and 2 studies

Safety observations made in the 4 Phase 1 reference studies, including 1 single and 3 repeated ascending-dose studies, which evaluated rimonabant (up to 300 mg single dose, up to 80 mg dose repeated for up to 7 days, and up to 60 mg dose repeated for up to 28 days) compared with placebo in young healthy male and female subjects, were the basis for selecting rimonabant doses to be further tested in patients. In the single dose

"first in man" study, the dose of 300-mg was reached without any serious tolerability issue (only minor and reversible AEs being reported). For multiple doses, 80 mg daily given for 7 days was associated with an increased incidence of events suggestive of a CNS impact in comparison with the previously tested 60-mg dose. After completion of this study, the good tolerability of this 60-mg dose was confirmed over a longer exposure of 28 days (ECG Phase 1 study).

In the multiple dose studies (pooled for this purpose), AEs were reported in 4 main SOCs CNS, GI, psychiatric, and general). The individual AEs more frequently reported with rimonabant when compared to placebo were: GI (nausea, vomiting, and abdominal pain), nervous system (dizziness, paresthesia, tremor, and disturbance in attention), psychiatric (anxiety, insomnia, and nervousness) and general (asthenia/fatigue). There were 4 SAEs reported out of 1048 healthy subjects (flank pain, transient paranoid reaction post marijuana intake, prostate cancer, and post-trauma vertebral compression fracture). Fifteen subjects prematurely discontinued rimonabant versus 10 subjects in the placebo group, showing no particular pattern of events.

From the Phase 2 program, the clinical safety profile of rimonabant 5-, 10-, 20-, or 40-mg, administered up to 24 weeks in patients with various conditions, showed events of the same nature as those reported in the Phase 1 studies. In addition, cases of depression were newly reported in this patient population, particularly from 3 studies involving alcohol-dependent patients, smokers, or obese patients. A majority of the SAEs reported in the Phase 2 studies could be linked to either underlying diseases or to the conditions being treated (schizophrenia or alcoholism). None were fatal. Comparable incidences of treatment discontinuation were noted between rimonabant 5-, 10-, or 20-mg groups and the placebo group [Table (7.4.1.1) 1], while a higher rate in comparison to placebo was noted in the studies conducted in obese patients and smokers receiving 40-mg. In any Phase 2 study, AEs resulting in discontinuation were from the GI, psychiatric, or nervous system disorders SOCs.

Table (7.4.1.1) 1 - Phase 2 studies - discontinuations due to AEs

		Rimonabant			
Study Name	**Placebo**	**5 mg**	**10 mg**	**20 mg**	**40 mg**
PDY3796	0%	-	-	-	4.3%
DRI3388	6.8%	4.5%	4.4%	1.4%	-
DRI5747	7.6%	5.3%	9.2%	4.5%	-
ACT4389	5.5%	-	-	-	20.8%
ACTOL	9.4%	-	-	6.1%	-
METATRIAL	11.2%	-	-	12.5%	-

7.4.1.2 Phase 3 studies

The primary focus of this briefing document is to present the data from the obesity and diabetes programs. Global pooling is presented for rare events, and the smoking cessation program is discussed where the profile of safety is different from that observed in the obesity program.

7.4.1.2.1 Most common adverse events

In the obesity studies, the AEs most commonly reported (≥2% of patients) during rimonabant administration and with a higher frequency than placebo were primarily GI (nausea/vomiting), nervous system (dizziness), or psychiatric (insomnia, mood alterations, or depressive disorders) [Table (7.4.1.2.1) 1]; trends towards a dose-relationship effect were noted for all of these events with the exception of insomnia. In the diabetic population, the events were of same nature when compared to the obese population as a whole [Table (7.4.1.2.1) 2]. In addition, possible condition-related events (eg, hypoglycemia), and additional events such as paresthesia or muscle spasms were more frequent in this population; these were observed at lower rates in the total obese population.

In the population of smokers, a similar safety profile was observed with rimonabant, with some differences in the nature or frequency of events that could be explained by the differences in the condition being treated (eg, minor infections or disturbance in attention reported by smokers) [Table (7.4.1.2.1) 3].

Table (7.4.1.2.1) 1 - Obesity program - AEs reported in ≥2% in the rimonabant 20-mg group and ≥1% over placebo

	Placebo (N=2474) %	**Rimonabant 5 mg (N=2520) %**	**Rimonabant 20 mg (N=2742) %**
Gastrointestinal disorders			
Nausea	4.7	6.9	13.6
Diarrhea	5.8	7.5	7.7
Vomiting	2.3	3.0	4.7
Nervous system disorders			
Dizziness	4.1	5.9	7.3
Psychiatric disorders			
Anxiety	2.1	2.9	5.9
Insomnia	3.4	3.2	5.8
Mood alterations with depressive symptoms	2.8	3.6	4.7
Depressive disorders	1.7	2.8	3.9
Miscellaneous			
Influenza	9.1	9.2	10.3
Asthenia/fatigue	4.4	5.0	6.1
Contusion	1.1	1.9	3.1
Hot flush	0.8	1.3	2.0

N= patients exposed to treatment at any time.

Table (7.4.1.2.1) 2 - Type 2 diabetes program - AEs reported in ≥2% in the rimonabant 20-mg group and ≥1% over placebo

	Placebo (N=488) %	**Rimonabant 20 mg (N=477) %**
Gastrointestinal disorders		
Nausea	5.5	11.3
Diarrhea	5.9	7.1
Vomiting	1.8	5.5
Nervous system disorders		
Dizziness	4.3	9.6
Paresthesia	0.8	2.9
Psychiatric disorders		
Mood alterations with depressive symptoms	2.7	6.1
Anxiety	2.9	5.2
Insomnia	2.0	4.6
Miscellaneous		
Asthenia/Fatigue	3.9	7.1
Arthralgia	4.5	5.7
Hypoglycemia	1.4	4.0
Muscle spasms	0.6	2.7

N= patients exposed to same treatment throughout entire study

Table (7.4.1.2.1) 3 - Smoking cessation program - AEs reported in ≥2% in the rimonabant 20-mg group and ≥1% over placebo

	Placebo (N=789) %	**Rimonabant 5 mg (N=2210) %**	**Rimonabant 20 mg (N=3884) %**
Gastrointestinal disorders			
Nausea	5.0	9.1	19.7
Diarrhea	4.5	7.6	10.4
Vomiting	1.6	1.8	4.8
Nervous system disorders			
Headache	10.9	12.6	12.3
Dizziness	3.9	5.0	8.1
Disturbance in attention	1.5	1.9	3.8
Psychiatric disorders			
Insomnia	6.9	7.9	9.9
Anxiety	2.9	3.6	5.6
Mood alterations with depressive symptoms	3.2	3.5	5.0
Somnolence	0.6	2.3	3.1
Abnormal dreams	0.7	1.0	2.3
Miscellaneous			
Irritability	3.3	6.8	8.0
Asthenia/fatigue	3.4	5.5	7.1
Decreased appetite	1.0	1.8	4.5
Hot flush	0.4	1.5	2.4
Anorexia	0.6	1.4	2.2

N= patients exposed to treatment at any time.

7.4.1.2.2 Serious adverse events

In the obesity program, there were roughly similar rates of patients with any SAEs across treatment groups [Table (7.4.1.2.2) 1]. These events were observed in similar SOCs with a low and comparable incidence across groups, with the exception of psychiatric disorders, wherein there were numerical differences across groups (Section 7.5). Specifically, in the diabetes population, a higher frequency of SAEs was observed in each treatment group: 36 cases (7.5%) in the rimonabant 20-mg group and 20 cases (4.1%) in the placebo group. When considering the global pooling of obesity and smoking cessation studies, the rates of SAEs were respectively: 3.6% in the rimonabant 20-mg group, 3.8% in the rimonabant 5-mg group, and 3.9% in the placebo group.

Table (7.4.1.2.2) 1 - Obesity program - incidence of SAEs displayed by SOC reported in ≥0.5% in the rimonabant 20-mg group and over placebo

n (%)	Placebo (N=2474)		Rimonabant 5 mg (N=2520)		Rimonabant 20 mg (N=2742)	
Any SAEs	*106*	*(4.3)*	*153*	*(6.1)*	*175*	*(6.4)*
Neoplasms benign, malignant	15	(0.6)	22	(0.9)	27	(1.0)
Infections & Infestations	13	(0.5)	15	(0.6)	21	(0.8)
Injury & procedural complications	8	(0.3)	17	(0.7)	20	(0.7)
Gastrointestinal disorders	13	(0.5)	14	(0.6)	18	(0.7)
Psychiatric disorders	2	(<0.1)	6	(0.2)	15	(0.5)

N= patients exposed to treatment at any time.
SAEs displayed by SOC reported in ≥0.5% in the rimonabant 20-mg group and over placebo

Individual SAEs, remained rarely (<0.1%) or infrequently (between 0.1% and 0.3%) reported in each group. The following SAEs were numerically more frequently reported in rimonabant-treated patients than placebo [Table (7.4.1.2.2) 2]:

- Traumatic fractures were reported in 14 rimonabant-treated patients in the context of fall (N=5 accidental falls in the 5-mg group, and N=2 accidental falls and N=1 fall secondary to vasovagal syncope in the 20-mg group) or road traffic accident (N=6 in the 20-mg group). All patients were hospitalized. When looking at any AE terms containing the text "fracture," the frequency remained the same across treatment groups: ie, 1.8% (including 0.2% of serious cases) in the rimonabant 20-mg group, 2.0% (including 0.1%) in the rimonabant 5-mg group, and 2.3% (including 0.1%) in the placebo group;
- Road traffic accidents occurred in 7 rimonabant-treated patients of whom 5 had no responsibility in the onset of the accident (2 were passengers [one was fatal] and 3 were drivers hit by another vehicle). In the remaining 2 cases, a syncopal episode due to hypoglycemia in a diabetic patient, and sleepiness in the other case, were at the origin of the accident;
- Uterine leiomyoma led to hospitalization in 11 cases and were surgically treated. The remaining 2 cases were assessed by the Investigator as “medically important.” When considering the overall incidence of uterine leiomyoma in the global pooling, the rates

were comparable across treatment groups: 0.2% in the rimonabant 20-mg group, 0.3% in the rimonabant 5-mg group, and 0.1% in the placebo group.

Table (7.4.1.2.2) 2 - Obesity program - incidence of individual SAEs

n (%)	Placebo (N=2474)		Rimonabant 5 mg (N=2520)		Rimonabant 20 mg (N=2742)	
Traumatic fractures	1	(<0.1)	5	(0.2)	9	(0.3)
Depressive disorders	1	(<0.1)	2	(<0.1)	8	(0.3)
Road traffic accident	1	(<0.1)	0	(0.0)	7	(0.3)
Uterine leiomyoma	0	(0.0)	8	(0.3)	5	(0.2)

N= patients exposed to treatment at any time.
SAEs reported in at least 5 patients in the rimonabant 20-mg group and over placebo

Overall, 18 fatal outcomes were reported in the rimonabant clinical program, completed as of 01 March 2007; 4 cases were off drug and 14 cases occurred during the study treatment period. Of the 14 cases that occurred during study treatment, 10 were observed in the obesity studies with similar rates across treatment groups (0.15% in the rimonabant 20-mg group, 0.12% in the rimonabant 5-mg group, and 0.12% in the placebo group) [Table (7.4.1.2.2) 3], 1 case of subdural hemorrhage was observed in the SERENADE study (diabetic study) in the placebo group, and the 3 others occurred during the smoking cessation studies (2 in the rimonabant 20-mg group: coronary artery sclerosis and road traffic accident, and 1 cardio-respiratory arrest in the placebo group). Thus, deaths were equally distributed across treatment groups, and did not show any specific pattern.

Table (7.4.1.2.2) 3 - Obesity program - fatal treatment-emergent SAEs

Reason for death	Placebo (N=2474)	Rimonabant 5 mg (N=2520)	Rimonabant 20 mg (N=2742)
Fatal SAEs	*3 (0.12)*	*3 (0.12)*	*4 (0.15)*
Cardiac arrest*	-	1	-
Cardiac failure	-	-	1
Coronary artery disease	-	-	1
Cerebral hematoma/CVA	1	-	-
Cerebral hemorrhage	1	-	-
Pulmonary embolism	1	-	-
Septic shock	-	1	-
Completed suicide**	-	1	-
Road traffic accident (as passenger)	-	-	1
Uterine cancer (end-stage)	-	-	1

N= patients exposed to treatment at any time.
* a 19-year-old female who had a prolonged Distance in time on the ECG tracing from the start of the QRS-complex to the end of the T-wave (QT) at baseline prior to any study drug intake, experienced a sudden cardiac arrest approximately 5 months after introduction of rimonabant 5-mg per day. Autopsy showed no cardiac lesions and a pre-existing long QT syndrome was suspected as a likely cause of death.
** see (Section 7.5.1.2)

7.4.1.2.3 Discontinuations due to adverse events

In the obesity program, the primary reasons for discontinuing rimonabant reflected the common safety profile of the drug and the requirement to discontinue for antidepressant treatment. Psychiatric (mood alterations, depressive disorders, anxiety, and insomnia), nervous system (dizziness), or GI (nausea) events resulted in premature discontinuation more frequently with rimonabant treatment than with placebo treatment; however, individual rates of events remained low.

These findings were confirmed by the post-adjudication assessment, conducted by an independent external committee that classified the reasons for discontinuation blinded to the treatment assignments. The findings of the committee did not modify the differences between rates observed across groups in the original assessment made by the Investigators [Table (7.4.1.2.3) 1].

Table (7.4.1.2.3) 1 - Obesity program - post-adjudication committee (Adj) assessment of discontinuations due to AEs * (versus original reason as per the Investigators)

	Placebo (N=2474) %		**Rimonabant 5 mg (N=2520) %**		**Rimonabant 20 mg (N=2742) %**	
PTs	**Adj.**	**Investig.**	**Adj.**	**Investig.**	**Adj.**	**Investig.**
Patient discontinuations due to AEs	*12.1*	*7.6*	*17.5*	*11.0*	*20.6*	*15.5*
Depressive disorders	1.2	1.0	2.0	1.5	2.5	2.3
Nausea	<0.1	<0.1	0.6	0.2	1.7	1.5
Anxiety	0.4	0.2	0.7	0.3	1.5	1.2
Mood alterations with depressive symptoms	1.1	0.7	1.7	1.0	1.8	1.2
Dizziness	0.2	0.1	0.2	0.2	0.8	0.7
Pregnancy**	0.4	0.4	1.3	1.3	0.7	0.7
Headache	0.5	0.3	0.6	0.4	0.6	0.5
Insomnia	0.4	0.2	0.2	0.1	0.5	0.4
Irritability	<0.1	<0.1	0.2	0.2	0.5	0.4
Diarrhea	0.2	0.1	0.4	0.2	0.5	0.3
Asthenia/fatigue	0.4	0.2	0.4	0.3	0.6	0.3

N= patients exposed to treatment at any time.

* events reported in ≥0.5% in the rimonabant 20-mg group;

** pre-defined withdrawal criterion as per protocols.

7.4.2 Safety from ongoing clinical studies

Safety data from ongoing studies include SAEs collected as of 01 March 2007, involving a total of 14 280 subjects in 11 ongoing studies which corresponds to new subjects/patients. These ongoing studies had a 1:1 randomization placebo to rimonabant 20-mg, resulting in an estimate of 7855 patient-years of which 3927 apply to rimonabant 20-mg.

All cases remain blinded to the treatment code, with the exception of serious and unexpected and possibly related cases, which were individually unblinded for regulatory expedited reporting to the Health Authorities.

A total of 893 out of 14 200 patients (6.3%) experienced SAEs after randomization in ongoing Phase 3 studies; none occurred in the Phase 1 studies. Consistently with the cumulative safety experience from rimonabant studies, SAEs were mainly of infectious or GI (1.0% and 0.9%, respectively), general (0.7%), nervous system (0.5%), or psychiatric (0.5%) origin. A review of suicidality-related events and seizures is detailed in Sections 7.5.1 and 7.5.2, respectively.

Eighteen post-randomization SAEs (<0.1%) in the ongoing Phase 3 studies had a fatal outcome secondary to concomitant illnesses or underlying diseases (eg, esophageal carcinoma or sepsis with multiple organ failure). There was a completed suicide which is presented in Section 7.5.1.2.

A total of 420 patients (3.0%) permanently discontinued the blinded study drug due to AEs, of whom 126 patients (0.9%) discontinued due to SAEs. The main reason for permanent treatment discontinuation was serious psychiatric disorders (37 cases, 0.3%), mainly depression (18 cases, 0.1%).

Thus, there were no new relevant safety findings identified in ongoing studies, compared to the known safety profile in the completed studies; although no formal conclusion can be made based on blinded data.

7.5 Adverse events of interest

7.5.1 Psychiatric events

The ECS has been implicated in the modulation of emotional processes, but the literature reports apparent contradictory results with rimonabant; the drug was found to display anxiolytic- or antidepressant-like effects, whereas others have reported an absence of effect or even an anxiogenic-like profile of the compound. Environmental factors such as baseline levels of stress as well as species differences and the doses used may account for these discrepancies (55).

7.5.1.1 Anxiety disorders

Anxiety disorders and symptoms included various manifestations of anxiety (such as anxiety, nervousness, panic attack, or panic reaction), with higher incidences in the rimonabant groups when compared with the placebo group, and trends towards a dose-relationship effect between 5- and 20-mg doses of rimonabant for anxiety symptoms and panic disorders [Table (7.5.1.1) 1].

Table (7.5.1.1) 1 - Obesity programs - anxiety disorders and symptoms

ANXIETY DISORDERS AND SYMPTOMS n (%)	Obesity studies					
	Placebo (N=2474)		5 mg (N=2520)		20 mg (N=2742)	
Anxiety disorders & symptoms	*100*	*(4.0)*	*141*	*(5.6)*	*278*	*(10.1)*
Anxiety symptoms	95	(3.8)	130	(5.2)	246	(9.0)
Panic disorders	1	(<0.1)	4	(0.1)	23	(0.8)
Specific and social phobic disorders	2	(<0.1)	0	(0.0)	5	(0.2)
Stress disorders	2	(<0.1)	7	(0.3)	6	(0.2)
Anxiety disorders nec	1	(<0.1)	1	(<0.1)	3	(0.1)
Fear symptoms	0	(0.0)	0	(0.0)	1	(<0.1)

N= patients exposed to any treatment throughout entire study

"Anxiety disorders and symptoms" were nonserious in the large majority of cases. Among the 419 cases, 3 cases were hospitalized and one was assessed by the Investigator as a "medically important" event. They did necessitate corrective treatment (mostly anxiolytics) in about the same proportion of patients across groups. They occurred earlier in the rimonabant 20-mg group (median of 83 days) when compared with the placebo group (median of 117 days), and remained transient (median recovery of 1 month in the rimonabant 20-mg versus 2 months in placebo).

Recovery was noted in the majority of patients while continuing their study treatment and whether or not they received corrective treatment.

In conclusion, anxiety disorders were predominantly short episodes of anxiety occurring during the first 3 months of rimonabant treatment. Almost all cases were nonserious, ie, not requiring hospitalization, and resolved while maintaining treatment in the majority of cases.

7.5.1.2 Depressive events and suicidality

Overall, depressive events were more frequent in the rimonabant 20-mg group when compared to the placebo group in the obesity and smoking programs, and were the main AEs leading to discontinuation. In addition, antidepressant treatment warranted mandatory treatment discontinuation as prespecified by the protocols.

Monitoring

A specific monitoring of mood levels was implemented during the conduct of the RIO and STRATUS studies.

In the RIO program, any patient with symptoms of depression was referred to a psychiatrist to determine the exact diagnosis using the Diagnostic and Statistical manual of Mental Disorders Fourth Edition (DSM-IV) criteria. In addition, a specific patient self-assessment, the HAD score, was completed regularly to help the Investigator identify additional potential cases, using a cut-off of the HAD depression subscore of ≥11 as the best estimate of "definite cases." The HAD scale, a 14-item scale (2 subscales with 7 items each, covering symptoms of depression and anxiety) was considered as appropriate for this purpose, because it is a reliable and extensively validated instrument to test mood level in medical outpatients, including obese patients and non psychiatric populations (52).

The repeated HAD evaluations may have induced a higher reporting of depression and anxiety events.

Table (7.5.1.2) 1 presents depressive-mood disorders and disturbances in the obesity and smoking cessation programs. The most frequently reported AEs were depressed mood, depression, depressive symptoms, and major depression.

Table (7.5.1.2) 1 - Number (%) of patients with depressed mood disorders and disturbances and mood disorders and disturbances (≥0.1%) in obesity and smoking cessation studies

	Obesity studies			Smoking cessation studies		
	Placebo (N=2474) n(%)	**5 mg (N=2520) n (%)**	**20 mg (N=2742) n (%)**	**Placebo (N=1453) n (%)**	**5 mg (N=2869) n (%)**	**20 mg (N=4567) n (%)**
Depressed mood disorders and disturbances	112 (4.5)	158 (6.3)	231 (8.4)	63 (4.3)	123 (4.3)	261 (5.7)
Depressive disorders	43 (1.7)	70 (2.8)	106 (3.9)	17 (1.2)	24 (0.8)	37 (0.8)
Depression	34 (1.4)	56 (2.2)	87 (3.2)	13 (0.9)	14 (0.5)	29 (0.6)
Dysthymic disorder	0 (0)	7 (0.3)	4 (0.1)	0 (0)	2 (<0.1)	0 (0)
Major depression	9 (0.4)	7 (0.3)	15 (0.5)	4 (0.3)	8 (0.3)	7 (0.2)
Postpartum depression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<0.1)
Mood alterations with depressive symptoms	70 (2.8)	91 (3.6)	129 (4.7)	47 (3.2)	101 (3.5)	229 (5.0)
Anhedonia	1 (<0.1)	0 (0)	3 (0.1)	0 (0)	1 (<0.1)	7 (0.2)
Decreased interest	1 (<0.1)	0 (0)	0 (0)	0 (0)	1 (<0.1)	5 (0.1)
Depressed mood	57 (2.3)	76 (3.0)	96 (3.5)	43 (3.0)	82 (2.9)	188 (4.1)
Depressive symptom	14 (0.6)	15 (0.6)	29 (1.1)	2 (0.1)	11 (0.4)	19 (0.4)
Feeling of despair	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)	3 (<0.1)
Tearfulness	0 (0)	0 (0)	4 (0.1)	1 (<0.1)	7 (0.2)	16 (0.4)

N= patients exposed to any treatment throughout entire study

Description of depressive events

In order to better analyze the depressive AEs, they were grouped according to the MedDRA hierarchy: *depression, major depression, and dysthymic disorders* were coded per MedDRA "depressive disorders"; and *depressed mood, depressive symptoms, feeling of despair, anhedonia, and decreased interest* were coded per MedDRA "mood alterations with depressive symptoms."

Depressive disorders

In the obesity program, depressive disorders (depression, major depression, and dysthymic disorders) were reported more frequently in the rimonabant 20-mg group compared with the placebo group. However, the characteristics of these events were similar between the treatment groups. They occurred early after treatment start (median time to onset: 3 months). Around 70% of patients required corrective treatment (placebo: 31/43; rimonabant 5-mg: 48/70; rimonabant 20-mg: 76/106) and the rate of discontinuation due to depressive disorders was around 60% (placebo: 25/43; rimonabant 5-mg: 39/70; rimonabant 20-mg: 64/106). Of note, a specific discontinuation rule was implemented in the RIO studies concerning antidepressant therapy, due to the potential effect on weight. In the smoking program, there was no imbalance between rimonabant and placebo.

Mood alterations

Mood alterations (depressed mood, depressive symptoms, feeling of despair, anhedomia, and decreased interest) were reported more frequently in the rimonabant 20-mg group when compared with the placebo group in the obesity program. Contrary to what was observed for depressive disorders, most patients with mood alterations were not treated (corrective therapy in rimonabant 20-mg: 28.7% versus placebo: 34.8%) and 75% of the patients continued the study drug.

Eight cases of depressive disorders and no case of mood alteration met a seriousness criterion in the rimonabant 20-mg group. Four of these 8 cases were hospitalized and the 4 other were considered by the Investigator to be medically important. Five of the 8 patients had a prior history of depression/anxiety symptoms and 5 of the 8 patients also had significant stressors. All 8 patients were discontinued and 7 of them received corrective therapy (antidepressants). From the most recent information, the outcome was favorable in 7 cases. One patient was still depressed at the last contact (9 months after the end of study).

Population and risk factors

The population included in the obesity studies is well representative of the general obese population in terms of psychiatric history or comorbidities, with a similar proportion of patients in both the rimonabant 20-mg and the placebo groups with a prior history of depressed mood disorders (rimonabant 20-mg: 9% and placebo: 8%) and suicidal and self-injurious behaviors (rimonabant 20-mg: 8 patients and placebo: 5 patients) [Table (7.5.1.2) 2].

Table (7.5.1.2) 2 - Number of patients with a psychiatric event among patients with past psychiatric history in the obesity studies

Psychiatric events	Placebo N (%)	Rimonabant 5 mg N (%)	Rimonabant 20 mg N (%)
Anxiety disorders and symptoms	112 (4.5)	103 (4.1)	100 (3.6)
Depressed mood disorders and disturbances	201 (8.1)	214 (8.5)	249 (9.1)
Suicidal and self-injurious behaviors nec + PT depression suicidal	5 (0.2)	1 (<0.1)	8 (0.3)

N= Exposed patients taking into account any patient exposition

Prior history of depressive disorders is the main risk factor that has been identified (8-fold, whatever the group) for depressive disorders: anxiety, insomnia, and mood alterations. This group of patients was also found to be at higher risk for other psychiatric disorders [Table (7.5.1.2) 3].

Table (7.5.1.2) 3 - Number (%) of patients with psychiatric adverse events >2% among patients with past medical history for depressive disorders - randomized and exposed patients in the obesity studies

Primary System Organ Class Grouped term	Obesity studies Placebo (N=192) n (%)	5 mg (N=206) n (%)	20 mg (N=235) n (%)
Psychiatric Disorders			
Any event	55 (28.6)	64 (31.1)	108 (46.0)
Depressive disorders	17 (8.9)	22 (10.7)	45 (19.1)
Anxiety	7 (3.6)	18 (8.7)	29 (12.3)
Insomnia	13 (6.8)	9 (4.4)	20 (8.5)
Mood alterations with depressive symptoms	11 (5.7)	17 (8.3)	19 (8.1)
Stress	6 (3.1)	5 (2.4)	7 (3.0)

To a lesser extent, other risk factors were also identified: higher in females versus males, in young versus the elderly, and in weight loss responders. Morbid obesity was not associated with an increased risk with rimonabant 20-mg contrary to placebo.

HAD depression subscore

The HAD depression subscore provides a cross-sectional overview at various time points of the mood state of the patients included in the RIO studies. The mean baseline was low in both the placebo (3.0) and rimonabant 20-mg (2.9) groups, reflecting the normal mood level in this population.

No changes from baseline in mean HAD depression subscore were observed in any treatment group during Year 1 (placebo: 3.0 and rimonabant 20-mg: 2.9) or Year 2, as there were no changes in mean scores across groups at any successive visit scheduled during Year 1 for all 4 RIO studies, or during Years 1 and 2 for 2 RIO studies. There was no difference between the rimonabant 20-mg and placebo groups for the percentage of patients who shifted to a higher score, regardless of the baseline score [Table (7.5.1.2) 4]. However, the HAD depression subscore in patients who experienced depressive disorders was sensitive to mood changes with a mean worst value that increased from 6.7 to 11.4 (placebo group) and from 5.4 to 12.3 (rimonabant 20-mg group).

Table (7.5.1.2) 4 - HAD - shift table for depression subscore - 1-year pooled RIO studies

Depression subscore Baseline status - Post baseline status	Placebo (N=1602) n/N (%)		Rimonabant 5 mg (N=2520) n/N (%)		Rimonabant 20 mg (N=2503) n/N (%)	
<=7						
<=7	781/892	(87.6)	1253/1413	(88.7)	1235/1410	(87.6)
8 – 10	75/892	(8.4)	116/1413	(8.2)	114/1410	(8.1)
>=11	36/892	(4.0)	44/1413	(3.1)	61/1410	(4.3)
8 – 10						
<=7	25/64	(39.1)	45/102	(44.1)	42/106	(39.6)
8 – 10	21/64	(32.8)	44/102	(43.1)	39/106	(36.8)
>=11	18/64	(28.1)	13/102	(12.7)	25/106	(23.6)
>=11						
<=7	3/12	(25.0)	6/23	(26.1)	10/29	(34.5)
8 – 10	3/12	(25.0)	7/23	(30.4)	9/29	(31.0)
>=11	6/12	(50.0)	10/23	(43.5)	10/29	(34.5)

Note: patients with baseline and postbaseline values.
Pooled data from studies: RIO-Europe, RIO-Lipids, RIO-Diabetes and RIO-North America.

Suicidality-related events in completed studies

A potential complication of depressive events is suicide and suicide attempt. To evaluate this risk in patients treated with rimonabant, a specific analysis was performed by the Sponsor of the cases of suicide, suicide attempt, or suicide ideation reported as AEs or associated symptoms to a psychiatric AE.

In addition the methodology developed at Columbia University by Dr. Kelly Posner (56),(57) and recommended by the FDA to assess suicidality risk was used to assess this potential risk in patients treated with rimonabant. This blinded analysis, performed at Columbia University, provided results similar to the Sponsor methodology, and is presented below.

The C-CASA method is based on a blinded classification of cases according to the following categories of interest:

	Category
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
9	Not enough information (non fatal)

The C-CASA methodology is now well validated and was used for the assessment of "suicidality" of antidepressant drugs and presented at the corresponding advisory committees (13 to 14 September 2004 and 13 December 2006).

The categories of interest, as per FDA recommendations, are definite suicidal cases including suicidal behavior (codes 1+2+3), suicidal ideation (code 4), and possible suicidal cases (codes 5+6+9).

The selection of cases is based on specific searches of string text in the clinical databases. The studies of interest had to be double-blind, randomized, placebo-controlled, completed trials, enrolling at least 20 patients or subjects per treatment arm. This search included all events that occurred during the double-blind phase of treatment, or within 60 days of stopping randomized treatment.

The following table displays the cases of suicidality in the obesity/diabetes indication [Table (7.5.1.2) 5].

Table (7.5.1.2) 5 - Suicidality assessment per C-CASA - number (%) of patients according to the first randomized treatment in the study - obesity/diabetes indication Phase 2 and 3 studies

	Placebo	Rimonabant			
	(N=2214) N (%)	5-mg (N=2720) N (%)	10 mg (N=198) N (%)	20 mg (N=3081) N (%)	40 mg (N=23) N (%)
Category					
1 Complete suicide	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2 Suicide attempt	0 (0)	0 (0)	0 (0)	1 (0.03)	0 (0)
3 Preparatory acts toward imminent suicide behavior	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4 Suicidal ideation	8 (0.36)	8 (0.29)	0 (0)	19 (0.62)	0 (0)
5 Self-injurious behavior, intent unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6 Not enough information (fatal)	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0)
9 Not enough information (nonfatal)	1 (0.05)	0 (0)	0 (0)	2 (0.06)	0 (0)

Phases III RIO studies, Phases IIIb, other studies: Binge Eaters, REBA (Eating behavior), EFC5745 and RIO ASIA and Phases II : obesity studies.

As an exact date was not always available for "suicidality" reported as associated symptoms, all events were displayed according to the first treatment received (whatever the re-randomization). This was the most conservative approach since all patients were re-randomized to a dose equal or below the initial dose. Of note, one patient in the 5-mg column had a suicidal ideation in a context of depression more than 5 months after re-randomization from 5-mg to placebo.

The cases of interest are the following:

Code 1: Completed suicide

- No case was identified according to C-CASA.

Code 2: Suicide attempt

One case was identified in the obesity program:

- Patient No 003388840112013 (14 days post-treatment with rimonabant 20-mg for 4 months) in a context of depression.

Code 3: Preparatory acts toward imminent suicide behavior

- No case was reported in the obesity/diabetes program.

Code 4: Suicidal ideation

- A total of 35 cases were assessed as suicidal ideation in the obesity and diabetes studies according to C-CASA. As shown in [Table (7.5.1.2) 5] there were more suicidal ideations in the rimonabant 20-mg group when compared with placebo in this indication (8 placebo, 8 rimonabant 5-mg, 19 rimonabant 20-mg).
- All cases were associated with a depressive disorder or an adjustment disorder. Approximately 40% of the cases whatever the treatment group had a prior history of depressive disorders or mood alterations and more than 70% had severe stressors. Only 3 patients were hospitalized (1 in placebo for bipolar disorder, and 2 in rimonabant 20-mg for depression and major depressive disorder [MDD]).

Code 5: Self-injurious behavior, intent unknown

- No case was identified.

Code 6: Not enough information

This case was reported by the Investigator: "complete suicide":

- Patient No. 004743840013019: rimonabant 5-mg.

Code 9: Not enough information (non-fatal)

- Cases were rare and equally balanced.

In the smoking program in the placebo-controlled short term studies, 2 cases of suicidal behavior were identified:

- Patient No 004474250007005 (placebo) – Code 2 "Suicide attempt";
- Patient No 004474826004023 (rimonabant 5-mg) about 13 days after treatment start – Code 3 "Preparatory acts toward imminent suicide bevhaviour".

Six cases, Code 4 "suicidal ideation," were also identified: 2 in placebo, 1 in rimonabant 5-mg, and 3 in rimonabant 20-mg.

In the STRATUS-WW study, where all patients were initially randomized to either rimonabant 5-mg or 20-mg, and subsequently re-randomized to a dose of rimonabant equal or lower or placebo, 2 cases of suicide behavior were identified:

- Patient No 004796840031191 (rimonabant 20/5-mg): Depressed mood started 5 months after the patient was switched from 20-mg to 5-mg. The patient attempted suicide 1 month after study drug discontinuation – Code 2 "Suicide attempt";
- Patient No 004796840019065 (rimonabant 20-mg) in a context of bipolar disorder 4 months after treatment start – Code 3 "Preparatory acts toward imminent suicide bevhaviour".

At least, in the CIRRUS study where all patients received rimonabant 20-mg, 1 case of suicide behavior was identified:

- Patient No 004798840013029 (rimonabant 20-mg): about 3 weeks after initiation of rimonabant 20-mg in combination with placebo patch in a non-placebo-controlled study – Code 2 "Suicide attempt".

Fourteen cases of suicidal ideation were assessed in these nonplacebo-controlled studies (smoking long-term) with an overall rate in the range of what was reported in placebo-controlled studies (0.34%).

Rimonabant was tested in early development in a small population of schizophrenic patients and also in weaned alcohol-dependent patients willing to remain abstinent. Twenty (20) were from these 2 studies equally distributed between placebo and rimonabant 20-mg (9 suicide attempt, 10 suicidal ideation, and 1 not enough information, non fatal).

Taking into account all indications and studies (placebo-controlled or not), based on C-CASA, 88 cases were assessed possibly (8) or definitely suicidal (80) in the Phase 2 and Phase 3 studies of the rimonabant development (including the recent SERENADE diabetic study), irrespective of the indication with no difference between placebo and rimonabant 20-mg, as presented in Table (7.5.1.2) 6.

Table (7.5.1.2) 6 - Suicidality assessment per C-CASA- Number (%) of patients according to the first randomized treatment in the study - Phase 2 and Phase 3 studies

	Placebo (N=3411) N (%)	Rimonabant 5 mg (N=5254) N (%)	Rimonabant 10 mg (N=198) N (%)	Rimonabant 20 mg (N=7851) N (%)	Rimonabant 40 mg (N=206) N (%)
Category					
1 Complete suicide	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2 Suicide attempt	7 (0.21)	0 (0)	0 (0)	6 (0.08)	0 (0)
3 Preparatory acts toward imminent suicide behavior	0 (0)	1 (0.02)	0 (0)	1 (0.01)	0 (0)
4 Suicidal ideation	14 (0.41)	10 (0.19)	0 (0)	41 (0.52)	0 (0)
5 Self-injurious behavior, intent unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6 Not enough information (fatal)	0 (0)	1 (0.02)	0 (0)	0 (0)	0 (0)
7 Self-injurious behavior, no suicidal intent	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
8 Other: accident; psychiatric; medical	227 (6.65)	440 (8.37)	8 (4.04)	638 (8.13)	4 (1.94)
9 Not enough information (nonfatal)	2 (0.06)	0 (0)	0 (0)	5 (0.06)	0 (0)

Phases III RIO studies, Phases III STRATUS studies, Phases III, other studies: Binge Eaters, REBA (Eating behavior), EFC5745, CIRRUS and RIO ASIA, and Phases II : Alcohol and schizophrenic studies, obesity and smoking studies.

Suicidality-related events in ongoing studies

In the ongoing studies, a specific questionnaire was implemented at every visit to specifically identify any cases of depressive-related events or other psychiatric disorders.

In case of depressive events and relevant psychiatric events, the patient is to answer the following question: *"Have you thought that life was not worth living or have you had urges to hurt yourself?"* and the Investigator had to indicate on a specific form whether or not suicidal ideation or suicide attempt were present.

All cases are to be reported as AEs.

As of 01 March 2007, 14 200 patients were exposed to the study drug in the ongoing Phase 3 studies with a balanced randomization corresponding to a total of 7855 patient-years.

A total of 53 cases (0.37%) of self-injurious behaviors, or "depression suicidal" as coded by MedDRA were reported. Since the studies are ongoing and information on cases is not yet complete, the C-CASA methodology has not been implemented. Among these cases, 24 were serious and were unblinded. They are displayed in [Table (7.5.1.2) 7]. (All cases of suicide or suicide attempt were unblinded).

Table (7.5.1.2) 7 - Serious cases of suicidal and self-injurious behaviors or depression suicidal reported prior to 01 March 2007 by Investigators in the ongoing Phase 3 studies

PT	Placebo	Rimonabant 20 mg
N	7100	7100
Suicide attempt	2	0
Completed suicide	-	1
Self-injurious ideation	-	1
Suicidal ideation	5	13
Depression suicidal	1	1
Total Patients	**8**	**16**

Studies EFC5823, EFC5827, EFC5828, EFC5826, EFC5107, EFC5593, EFC6001, PMC0172, EFC5749

In addition, 1 suicide attempt was reported as "no drug given"; and 1 suicide ideation was also reported more than 75 days after the end of treatment (placebo). After the cut off date, 1 suicide attempt and 1 suicide gesture were reported in 2 patients in the rimonabant 20-mg treatment group.

The nonserious cases include 1 depression suicidal, 1 intentional self-injury, and 27 suicidal ideation.

Thus, in the ongoing Phase 3b studies where the monitoring and prospective collection of suicidality data was intensive, there were no new relevant safety findings identified, compared to the known safety profile in the completed studies, although no formal conclusion can be made based on blinded data.

Conclusions of depressive events and suicidality

Rimonabant increased depressive-related events. Among these AEs, we can easily identify 2 different categories according to MedDRA:

- A category of mood disorders that were minor and where the patient recovered mostly without corrective treatment or instances of rimonabant discontinuation increased in both the obesity and the smoking programs, and
- Another category of depressive disorders that required antidepressant treatment more frequently in the obesity studies. This led to study discontinuation as specified in the protocol.

Both disorders occurred early with one-half of them occurring within 3 to 4 months in the rimonabant group. From the analysis of suicide and suicide attempt, the overall rate was low and balanced across treatment groups including placebo.

An imbalance was seen in suicidal ideation, mostly in the obesity studies. Suicide ideation did not occur in isolation and was always associated with depressive events or adjustment disorders, and was increased in the same proportion as these underlying events were in the rimonabant-treated patients when compared to placebo.

The studies confirmed that the population at risk for depressive events, whether with placebo or rimonabant, is the population with a prior history of depressive disorders, with more than 40% of the depressive events and suicidality occurring in this group of patients. This population was also found to be at higher risk of anxiety.

7.5.1.3 Other psychiatric events

This section covers other relevant psychiatric TEAEs reported in the obesity development program that are not presented in the other sections of this briefing document. These events, which include sleep disorders, perception disturbances, personality disorders, and sexual dysfunctions, are listed in Table (7.5.1.3) 1. Overall, sleep disorders were the most frequently reported events, and among them, insomnia was the most common.

Table (7.5.1.3) 1 - Other selected psychiatric events reported in ≥0.1% of the cases in rimonabant groups and more frequently than placebo - randomized and exposed patients - obesity studies

	Obesity studies		
	Placebo (N=2474) N (%)	**5 mg (N=2520) N (%)**	**20 mg (N=2742) N (%)**
Sleep disorders and disturbances			
Insomnia	77 (3.1)	74 (2.9)	152 (5.5)
Middle insomnia	2 (<0.1)	5 (0.2)	5 (0.2)
Abnormal dreams	3 (0.1)	1 (<0.1)	10 (0.4)
Nightmare	3 (0.1)	4 (0.2)	28 (1.0)
Sleep walking	0 (0)	0 (0)	6 (0.2)
Disturbances in thinking and perception			
Hallucination, visual	0 (0)	0 (0)	5 (0.2)
Personality disorders and disturbances in behavior			
Aggression	2 (<0.1)	6 (0.2)	9 (0.3)
Sexual dysfunctions, disturbances and gender identity disorders			
Loss of libido	0 (0)	1 (<0.1)	4 (0.1)

Obesity studies: EFC4733, EFC4735, EFC4736, EFC4743, EFC5031, EFC5745, ACT3801
AEs coded using MedDRA 9.0 version

Other cases were infrequently or even rarely reported (≤0.5%). Hallucinations were not serious and not associated with patterns of events evocative of risk of dependence. Cases reported in the other categories were not serious.

In addition, 2 cases of psychotic disorders were reported. One "transient psychotic disturbance" was serious and the patient recovered with corrective therapy while rimonabant was discontinued; the other was a delusional disorder with a past history of dissociative disorder still present at baseline.

7.5.2 Neurological events

7.5.2.1 Neurological events by categories (sensory changes, motor impairment, cognitive difficulties)

The review and analysis of neurological symptoms such as sensory changes, motor impairments, and cognitive difficulties was done using data from the 12 completed Phase 3 studies. It included additional information collected from the clinical sites during the retrospective documentation of the cases of neurological AEs, ie, the results of specialist consultations or complementary investigations performed during the course of the study or later. This was done on the safety population ("all exposed") as described in Figure (7.3) 1. Overall, sensory changes were the main events reported in each treatment group, followed by cognitive difficulties, and motor impairments [Table (7.5.2.1) 1].

Table (7.5.2.1) 1 - Neurological adverse events reported with an incidence of ≥1%

	Obesity studies			Obesity and Smoking cessation studies		
Neurological Symptoms: **SENSORY CHANGES**	**Placebo (N=2474) N (%)**	**5 mg (N=2520) N (%)**	**20 mg (N=2742) N (%)**	**Placebo (N=3927) N (%)**	**5 mg (N=5389) N (%)**	**20 mg (N=7309) N (%)**
Any Class - any event	310 (12.5)	403 (16.0)	554 (20.2)	469 (11.9)	869 (16.1)	1498 (20.5)
Sensory changes						
Any event	230 (9.3)	299 (11.9)	406 (14.8)	345 (8.8)	594 (11.0)	1001 (13.7)
Dizziness	101 (4.1)	148 (5.9)	200 (7.3)	157 (4.0)	292 (5.4)	568 (7.8)
Paresthesia	22 (0.9)	25 (1.0)	41 (1.5)	32 (0.8)	48 (0.9)	105 (1.4)
Dysgeusia	6 (0.2)	6 (0.2)	8 (0.3)	23 (0.6)	59 (1.1)	83 (1.1)
Hypoesthesia	21 (0.8)	35 (1.4)	39 (1.4)	33 (0.8)	53 (1.0)	68 (0.9)
Sciatica	16 (0.6)	23 (0.9)	34 (1.2)	19 (0.5)	27 (0.5)	40 (0.5)
Motor impairment						
Any event	57 (2.3)	68 (2.7)	93 (3.4)	79 (2.0)	119 (2.2)	200 (2.7)
Tremor	2 (<0.1)	6 (0.2)	24 (0.9)	7 (0.2)	21 (0.4)	76 (1.0)
Cognitive difficulties						
Any event	51 (2.1)	66 (2.6)	113 (4.1)	89 (2.3)	242 (4.5)	522 (7.1)
Disturbance in attention	12 (0.5)	4 (0.2)	15 (0.5)	34 (0.9)	59 (1.1)	189 (2.6)
Somnolence	5 (0.2)	12 (0.5)	14 (0.5)	14 (0.4)	77 (1.4)	157 (2.1)

A total of 2.2% of patients with neurological events permanently discontinued the study drug due to these AEs. The main neurological AEs leading to discontinuation were dizziness, paresthesia/hypoesthesias, tremor, and memory loss [Table (7.5.2.1) 2].

Table (7.5.2.1) 2 - Number (%) of patients with neurological adverse events leading to withdrawal occurring in ≥0.1% randomized and exposed patients - obesity phase 3 studies and overall phase 3 completed studies

Neurological Symptoms (including sensory changes, motor impairments, cognitive difficulties)	**Obesity studies**			**Obesity and Smoking cessation studies**		
	Placebo (N=2474) N (%)	**5 mg (N=2520) N (%)**	**20 mg (N=2742) N (%)**	**Placebo (N=3927) N (%)**	**5 mg (N=5389) N (%)**	**20 mg (N=7309) N (%)**
Any Class - any event	16 (0.6)	25 (1.0)	61 (2.2)	25 (0.6)	62 (1.2)	158 (2.2)
Sensory changes						
Any event	8 (0.3)	11 (0.4)	38 (1.4)	10 (0.3)	29 (0.5)	84 (1.1)
Dizziness	3 (0.1)	5 (0.2)	18 (0.7)	4 (0.1)	16 (0.3)	44 (0.6)
Paresthesia	1 (<0.1)	1 (<0.1)	9 (0.3)	1 (<0.1)	2 (<0.1)	16 (0.2)
Vertigo	0 (0)	2 (<0.1)	3 (0.1)	0 (0)	2 (<0.1)	5 (<0.1)
Motor impairments						
Any event	6 (0.2)	7 (0.3)	16 (0.6)	7 (0.2)	8 (0.1)	27 (0.4)
Tremor	0 (0)	2 (<0.1)	5 (0.2)	0 (0)	2 (<0.1)	8 (0.1)
Cognitive difficulties						
Any event	3 (0.1)	7 (0.3)	18 (0.7)	9 (0.2)	27 (0.5)	62 (0.8)
Disturbance in attention	3 (0.1)	0 (0)	4 (0.1)	5 (0.1)	6 (0.1)	25 (0.3)
Somnolence	0 (0)	2 (<0.1)	0 (0)	0 (0)	7 (0.1)	11 (0.2)
Confusional state	0 (0)	0 (0)	3 (0.1)	0 (0)	1 (<0.1)	7 (<0.1)
Amnesia	1 (<0.1)	2 (<0.1)	4 (0.1)	1 (<0.1)	4 (<0.1)	6 (<0.1)

Few patients reported serious neurological AEs and there were no imbalances between groups [Table (7.5.2.1) 3].

Table (7.5.2.1) 3 - Number (%) of patients with serious neurological adverse events (leading to hospitalization or classified by Investigators as medically important event) - obesity studies and obesity and smoking cessation studies

Neurological Symptoms (including sensory changes, motor impairments, cognitive difficulties)	Obesity studies			Obesity and Smoking cessation studies		
	Placebo (N=2474) N (%)	5 mg (N=2520) N (%)	20 mg (N=2742) N (%)	Placebo (N=3927) N (%)	5 mg (N=5389) N (%)	20 mg (N=7309) N (%)
Any Class - any event	14 (0.6)	13 (0.5)	15 (0.5)	16 (0.4)	16 (0.3)	20 (0.3)
Sensory changes						
Any event	4 (0.2)	3 (0.1)	4 (0.1)	4 (0.1)	3 (<0.1)	5 (<0.1)
Paresthesia	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	2 (<0.1)
Coordination abnormal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<0.1)
Dizziness	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Hypoesthesia	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Vertigo	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Carpal tunnel syndrome	1 (<0.1)	1 (<0.1)	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)
Complex regional pain syndrome	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)
Meniere's disease	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)
Cauda equina syndrome	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)
Gait disturbance	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)
Lumbar radiculopathy	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)
Motor impairments						
Any event	6 (0.2)	7 (0.3)	7 (0.3)	7 (0.2)	9 (0.2)	10 (0.1)
Transient ischemic attack	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Epilepsy	0 (0)	1 (<0.1)	2 (<0.1)	0 (0)	1 (<0.1)	2 (<0.1)
Cerebrovascular accident	1 (<0.1)	1 (<0.1)	0 (0)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Grand mal convulsion	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (<0.1)	1 (<0.1)
Ischemic stroke	0 (0)	1 (<0.1)	1 (<0.1)	0 (0)	1 (<0.1)	1 (<0.1)
Nervous system disorder	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Stress incontinence	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<0.1)
Urinary incontinence	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)
Cerebral infarction	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)
Embolic stroke	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)
Thalamic infarction	0 (0)	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)
Convulsion	1 (<0.1)	0 (0)	0 (0)	2 (<0.1)	0 (0)	0 (0)
Cerebral hematoma	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)
Cerebral hemorrhage	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)
Cerebral ischemia	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)
Eyelid ptosis	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)
Cognitive difficulties						
Any event	4 (0.2)	3 (0.1)	5 (0.2)	5 (0.1)	4 (<0.1)	6 (<0.1)
Syncope vasovagal	1 (<0.1)	1 (<0.1)	3 (0.1)	1 (<0.1)	2 (<0.1)	4 (<0.1)
Syncope	2 (<0.1)	2 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)	2 (<0.1)
Loss of consciousness	1 (<0.1)	0 (0)	0 (0)	1 (<0.1)	0 (0)	0 (0)

The sensory changes occurred more frequently in the rimonabant groups compared to placebo, mostly due to dizziness, both in the obese and in smokers [Table (7.5.2.1) 4].

Table (7.5.2.1) 4 - Number of patients (%) with adverse events within the category "sensory changes" (≥0.1%) - obesity studies and obesity and smoking cessation studies

	Obesity studies			Obesity and Smoking cessation studies		
Neurological Symptoms: SENSORY CHANGES	**Placebo (N=2474) N (%)**	**5 mg (N=2520) N (%)**	**20 mg (N=2742) N (%)**	**Placebo (N=3927) N (%)**	**5 mg (N=5389) N (%)**	**20 mg (N=7309) N (%)**
Any Class - any event	310 (12.5)	403 (16.0)	554 (20.2)	469 (11.9)	869 (16.1)	1498 (20.5)
Sensory changes						
Any event	230 (9.3)	299 (11.9)	406 (14.8)	345 (8.8)	594 (11.0)	1001 (13.7)
Dizziness	101 (4.1)	148 (5.9)	200 (7.3)	157 (4.0)	292 (5.4)	568 (7.8)
Paresthesia	22 (0.9)	25 (1.0)	41 (1.5)	32 (0.8)	48 (0.9)	105 (1.4)
Dysgeusia	6 (0.2)	6 (0.2)	8 (0.3)	23 (0.6)	59 (1.1)	83 (1.1)
Hypoesthesia	21 (0.8)	35 (1.4)	39 (1.4)	33 (0.8)	53 (1.0)	68 (0.9)
Sciatica	16 (0.6)	23 (0.9)	34 (1.2)	19 (0.5)	27 (0.5)	40 (0.5)
Vision blurred	8 (0.3)	9 (0.4)	17 (0.6)	13 (0.3)	23 (0.4)	40 (0.5)
Vertigo	10 (0.4)	11 (0.4)	20 (0.7)	14 (0.4)	19 (0.4)	35 (0.5)
Tinnitus	13 (0.5)	8 (0.3)	15 (0.5)	16 (0.4)	16 (0.3)	28 (0.4)
Carpal tunnel syndrome	12 (0.5)	15 (0.6)	17 (0.6)	14 (0.4)	21 (0.4)	23 (0.3)
Dizziness postural	3 (0.1)	3 (0.1)	5 (0.2)	6 (0.2)	6 (0.1)	13 (0.2)
Balance disorder	2 (<0.1)	3 (0.1)	9 (0.3)	2 (<0.1)	3 (<0.1)	11 (0.2)
Restless legs syndrome	0 (0)	3 (0.1)	4 (0.1)	1 (<0.1)	7 (0.1)	10 (0.1)
Vertigo positional	2 (<0.1)	2 (<0.1)	4 (0.1)	3 (<0.1)	6 (0.1)	9 (0.1)
Hypoesthesia facial	0 (0)	5 (0.2)	5 (0.2)	0 (0)	7 (0.1)	8 (0.1)
Parosmia	3 (0.1)	0 (0)	3 (0.1)	4 (0.1)	4 (<0.1)	8 (0.1)

Episodes of dizziness occurred more frequently in the rimonabant 20-mg group when compared with the placebo group. They generally started after a few weeks of treatment (median time to onset of 69 days) and the episodes were described by the patients as a sensation of being dizzy or lightheaded for a period of 2 to 3 weeks (median duration of 16 days). Few cases of presyncope (coded as dizziness) occurred. Most patients recovered without corrective therapy while the study drug was continued. The cases were more frequent in diabetic patients (9.6% in the rimonabant 20-mg group and 4.3% in the placebo group) and in elderly (>65 years) patients (15.3% in the rimonabant 20-mg group and 2.7% in the placebo group). Dizziness was mostly of mild or moderate intensity and led to study drug discontinuation in 9% of patients in the rimonabant 20-mg group compared to 3% in the placebo group. Dizziness was not associated with hypotension, orthostatic hypotension, hypoglycemia, or with falls.

Events commonly reported in the rimonabant groups also included paresthesia and dysesthesias (including hypoesthesias) (rimonabant 20-mg: 2.4% and placebo: 1.8%). Paresthesia and dysesthesias were slightly more frequent than hypoesthesias, and were generally described as paresthesia or tingling sensations. Hypoesthesias were generally described as numbness of the limbs, but a few cases were described as facial numbness or oral hypoesthesias. These events were transient, mostly mild, or moderate in intensity, and recovered without corrective therapy while rimonabant was continued. Paresthesias/ hypoesthesias led to study drug discontinuation in 13% of patients with paresthesia/ hypoesthesia in the rimonabant group (compared to 2.4% in the placebo group). They occurred after 2 to 3 months of treatment (median time to onset 101 days) and lasted a few

weeks (median duration 36 days), although some episodes were of longer duration. They generally recovered spontaneously without corrective therapy while the study drug was continued. Few patients had complementary investigations that were normal in most cases. Three cases of paresthesia or hypoesthesias in the 20-mg group led to hospitalization, of which 2 were related to transient ischemic attacks. Overall, there was no imbalance of transient ischemic attacks or cerebrovascular accidents between the 2 groups. Paresthesia was more frequent in diabetics: 2.9% in the rimonabant group versus 0.8% in the placebo group. Most cases were not typical of classical distal diabetic sensory neuropathy (sparing the lower limbs). In each study, any information about preexisting diabetic sensory neuropathy was captured only in the overall medical history collection and not during collection of disease-specific information; hence, it is difficult to know if any pretreatment disease was a risk factor for the paresthesias observed. Six of the 14 patients with TEAEs of paresthesia in the rimonabant group had concomitant medical conditions (ie, carpal tunnel syndrome, vitamin B_{12} deficiency, cardiovascular accident, rheumatoid arthritis) or concomitant medication (antiepileptic) that could have predisposed them to develop paresthesias.

Dysgeusia was frequently reported in smokers (1.6% in the rimonabant 20-mg group and 1.2% in the placebo group) and rarely reported in the obese, with no difference between groups.

Other events were rarely reported. The detailed analysis of the individual cases of potentially medically significant cases (eg, facial numbness, diplopia, nystagmus, scotoma, vestibular disorders), including the specialist consultations (eg, neurologists, ophthalmologist) and the results of the complementary investigations (eg, neuroimaging and neurophysiological testing) were carefully reviewed and individual cases were provided to the FDA in the complete response to the action letter.

Cognitive difficulties were more commonly reported in rimonabant groups and were dominated by disturbance in attention and somnolence/sedation/lethargy, which were more frequent in the smoking cessation program [Table (7.5.2.1) 5].

Table (7.5.2.1) 5 - Number of patients (%) with adverse events within the category "cognitive difficulties" (≥0.1%) - obesity studies and obesity and smoking cessation studies

	Obesity studies			**Obesity and Smoking cessation studies**		
Neurological Symptoms: COGNITIVE DIFFICULTIES	**Placebo (N=2474) N (%)**	**5 mg (N=2520) N (%)**	**20 mg (N=2742) N (%)**	**Placebo (N=3927) N (%)**	**5 mg (N=5389) N (%)**	**20 mg (N=7309) N (%)**
Any Class - any event	*310 (12.5)*	*403 (16.0)*	*554 (20.2)*	*469 (11.9)*	*869 (16.1)*	*1498 (20.5)*
Any event	51 (2.1)	66 (2.6)	113 (4.1)	89 (2.3)	242 (4.5)	522 (7.1)
Disturbance in attention	12 (0.5)	4 (0.2)	15 (0.5)	34 (0.9)	59 (1.1)	189 (2.6)
Somnolence	5 (0.2)	12 (0.5)	14 (0.5)	14 (0.4)	77 (1.4)	157 (2.1)
Lethargy	5 (0.2)	8 (0.3)	14 (0.5)	7 (0.2)	38 (0.7)	65 (0.9)
Memory impairment	8 (0.3)	14 (0.6)	17 (0.6)	11 (0.3)	24 (0.4)	43 (0.6)
Amnesia	9 (0.4)	11 (0.4)	23 (0.8)	9 (0.2)	16 (0.3)	42 (0.6)
Syncope vasovagal	9 (0.4)	8 (0.3)	13 (0.5)	10 (0.3)	11 (0.2)	19 (0.3)
Syncope	6 (0.2)	6 (0.2)	11 (0.4)	8 (0.2)	10 (0.2)	16 (0.2)
Confusional state	0 (0)	1 (<0.1)	4 (0.1)	0 (0)	4 (<0.1)	10 (0.1)
Disorientation	0 (0)	1 (<0.1)	4 (0.1)	0 (0)	5 (<0.1)	9 (0.1)

Disturbance in attention/cognitive disorders/mental impairment were primarily reported in the smoking cessation program (3.9% in the rimonabant 20-mg group and 1.5% in the placebo group), essentially as "disturbance in attention." They were mostly described as disturbance in attention that could be linked to nicotine withdrawal symptoms. In the obesity program, they were infrequently reported, with no difference between groups (rimonabant 20-mg: 0.5% and placebo: 0.5%). None of the cases led to hospitalization and few were severe in intensity. They rarely led to treatment discontinuation in any treatment group. In obese patients, disturbance in attention was rarely reported and when reported, a similar incidence in all treatment groups was observed.

Memory loss (amnesia/memory impairment*)* was reported as nonsevere cases of memory impairment, described as memory loss, forgetfulness, or short-term memory decrease for a period of 2 to 3 months (median duration of 91 days). Cases occurred earlier in the rimonabant 20-mg group (median time to onset of 64 days in the 20-mg group and 117 days in the placebo group). Most cases recovered without corrective therapy while the study drug was continued. Study drug was discontinued in 15% of patients with memory loss in the 20-mg group (12% in the placebo group). None of the cases led to hospitalization.

Somnolence/sedation/lethargy was primarily reported in the smoking cessation program (3.1% in the rimonabant 20-mg group and 0.6% in the placebo group). In the obesity program, the incidence of somnolence was 0.5% in the rimonabant 20-mg group and 0.2% in the placebo group, and no patient discontinued due to this event. These events were mostly described as somnolence, drowsiness, or daytime sleepiness. None of the cases led to hospitalization and few were severe in intensity. Patients recovered in most cases, and corrective therapy was similarly used across treatment groups.

In the obesity and smoking cessation programs, rare cases of confusion and disorientation were reported in the rimonabant groups. A total of 11 patients reported 14 episodes of confusion: 10 events occurred with rimonabant 20-mg and 4 with rimonabant 5-mg. None led to hospitalization. All cases recovered without corrective treatment, with the exception of 1 recurrent episode that was treated with sedatives/hypnotics and 1 event for which antihypertensive comedication was reduced. The time of onset was variable during the course of studies (a few days to 1.5 year), and the duration was generally short (a few days) or with intermittent episodes, if prolonged. Associated symptoms were mainly memory impairment, dizziness, and decreased concentration. Rimonabant was discontinued in more than half of the cases. None of the cases resulted in a complementary consultation/investigation, except 1 case associated with a trauma that led to an emergency room consultation. There was 1 patient with a past history of sleepwalking and another with a past history of resection of a brain tumor associated with seizures.

A total of 14 patients reported 14 episodes of disorientation: 9 events occurred with 20-mg rimonabant, and 5 occurred with 5-mg rimonabant. They occurred within the first few days or first few weeks of rimonabant intake, lasting a few hours or days. They were described as a transient loss of orientation, intermittent, infrequently associated with various symptoms like dizziness, lethargy, difficulty concentrating, irritability, nervousness, or euphoria. All events recovered without corrective treatment; rimonabant was discontinued in 4 cases. One episode in a 66 year-old female had a complementary investigation with a brain CT-scan, the result of which was within normal limits.

Events in the motor impairments category were reported comparably across treatment groups, with no marked differences in terms of incidences for individual PTs except tremor in both programs (1% in the rimonabant 20-mg group, 0.4% in the rimonabant 5-mg group, and 0.2% in the placebo group) [Table (7.5.2.1) 6].

Table (7.5.2.1) 6 - Number of patients (%) with AEs within the category "motor impairments"- obesity studies and obesity and smoking cessation studies

	Obesity studies			Obesity and Smoking cessation studies		
Neurological Symptoms: MOTOR IMPAIRMENTS	**Placebo (N=2474) N (%)**	**5 mg (N=2520) N (%)**	**20 mg (N=2742) N (%)**	**Placebo (N=3927) N (%)**	**5 mg (N=5389) N (%)**	**20 mg (N=7309) N (%)**
Any Class - any event	*310 (12.5)*	*403 (16.0)*	*554 (20.2)*	*469 (11.9)*	*869 (16.1)*	*1498 (20.5)*
Any event	57 (2.3)	68 (2.7)	93 (3.4)	79 (2.0)	119 (2.2)	200 (2.7)
Tremor	2 (<0.1)	6 (0.2)	24 (0.9)	7 (0.2)	21 (0.4)	76 (1.0)
Dysphonia	2 (<0.1)	6 (0.2)	5 (0.2)	4 (0.1)	8 (0.1)	14 (0.2)
Nerve compression	8 (0.3)	14 (0.6)	7 (0.3)	10 (0.3)	24 (0.4)	13 (0.2)
Urinary incontinence	5 (0.2)	8 (0.3)	7 (0.3)	5 (0.1)	8 (0.1)	11 (0.2)
Muscular weakness	4 (0.2)	1 (<0.1)	5 (0.2)	5 (0.1)	4 (<0.1)	10 (0.1)
Blepharospasm	1 (<0.1)	5 (0.2)	0 (0)	5 (0.1)	11 (0.2)	8 (0.1)

In the obesity program, tremor was usually described as mild or moderate tremor, shakiness, or tremulousness localized to extremities, and, exceptionally, as a full body tremor. Tremor occurred within the first months of introduction of rimonabant (median time to onset 90 days). One patient out of 5 with tremor discontinued rimonabant 20-mg. The other cases recovered while rimonabant was continued.

Other rare events were of various types, such as ischemic or hemorrhagic cerebral stroke, localized motor deficits, or other atypical neurological signs. They remained isolated or were reported in comparative proportions across groups. Of note, in RIO Lipids, a 51 year-old female patient in the 20-mg group, with hypertension and dyslipidemia, had short-term memory loss, dizziness, depressed mood, and blurred vision starting during the 2 first months of treatment, and numbness of the toes after 11 months of treatment. No complementary investigations were performed. The patient completed the study. Follow-up information collected more than 3 years after the end of the study revealed that the husband of the patient had reported to the clinical site that the blurred vision was due to progressive supranuclear palsy. No confirmation of this information is available.

A total of 3 cases of multiple sclerosis were reported in the clinical development program. Two cases of multiple sclerosis out of 2520 patients (<0.1%) were diagnosed during rimonabant 5-mg treatment. One case out of 2474 patients was reported in the placebo group, after the patient had reported diplopia:

- 1 case in the 5-mg group was published (58);
- 1 case in the 5-mg group was diagnosed only 1 month after treatment start.

No cases were reported in the rimonabant 20-mg group or during the second year of exposure. In addition, 1 patient in the 20-mg group with a medical history of multiple sclerosis presented an episode of diplopia related to his preexisting disease.

7.5.2.2 Seizures

7.5.2.2.1 Preclinical data

Two studies were conducted to address the proconvulsant potential of rimonabant using a mouse model of pentylenetetrazole (PTZ)-induced convulsions. In the first study, intraperitoneal (IP) administration of rimonabant, either acutely or subacutely at doses up to 10 mg/kg/day for 5 days, had no effect on the threshold intravenous dose of PTZ required to induce clonic convulsions. In the second study, acute oral administration of rimonabant at doses between 10 and 100 mg/kg exhibited a propensity, unrelated to dose, to potentiate tonic convulsions when combined with a dose of PTZ that alone induced clonic convulsions in 90% of mice. The data suggest that rimonabant has some degree of proconvulsant potential under the particular conditions of this model, although a molecule with clear convulsant properties would be expected to exhibit a dose-response.

In order to investigate the effects of rimonabant alone on neuronal excitability, studies were performed to evaluate the effects of acute and repeated treatment on the EEG in conscious, unrestrained rats. No abnormal patterns of EEGs, such as spikes, spikes-and-trains, or spike trains were noted following repeated IP administration of rimonabant to rats at doses up to 10 mg/kg/day for 1 month or 30 mg/kg/day for 14 days.

During the repeated-dose toxicity studies, convulsions that were short in duration and resolved without treatment were observed sporadically in mice, rats, and macaques. No convulsions were observed in dogs or rabbits. Characteristically, the convulsions appeared to be associated with the stress of handling for various procedures. There was no evidence of a relationship between the duration of treatment and convulsive activity.

Extensive histopathological investigations have unequivocally demonstrated an absence of neuropathological alterations in the brain of mice, rats, dogs, and macaques as a result of chronic administration of rimonabant.

These results indicate a weak proconvulsant potential for rimonabant in animals when combined with a chemical that alone induced convulsions or with stressful conditions (experimental procedures) in the repeat-dose toxicity studies in mice, rats, and macaques. Experimental data showed that rimonabant had no effect on neuronal excitability in

animals when administered alone. These data are consistent with the view that rimonabant is without proconvulsant potential in the absence of other stressors.

7.5.2.2.2 Clinical data

Completed studies

Patients with treated epilepsy were excluded from the clinical trials (RIO and STRATUS), however, patients with a previous history of seizures were permitted. In the RIO and STRATUS studies, 0.4% and 0.5% of patients, respectively, had histories of previous seizures.

In order to further evaluate the potential risk of seizures, an analysis was undertaken of all completed studies up to 01 March 2007. This analysis was carried out on completed studies from all phases (Phases 1, 2, and 3) at the cut-off date of 01 March 2007. Cases were identified based on HLGT "Seizures (incl. subtypes)" using MedDRA 9.0. In addition, a string search was performed on the available narratives of all rimonabant studies in the Pharmacovigilance database for the following key words: "convuls," "petit mal," "grand mal," "epilep," "tonic clonic," "focal," "partial," "generaliz," "absence," "conscious," "seizur," "ictus," "ictal," "clon."

A total of 19 cases were identified in the completed studies: 8 were observed during placebo administration/off drug period (including 2 during placebo run-in and 1 during an off-drug follow-up period 3 months after the last intake of drug), 2 during rimonabant 5-mg treatment, and 9 during rimonabant 20-mg treatment

The 19 cases were reviewed on a blinded basis by 2 external neurologists [Dr Baulac of Pitié-Salpêtrière Hospital, Paris VI University (FR) and Dr Mattson of Yale University School of Medicine (US)] to better establish the likelihood of diagnosis. The external experts received patient profiles blinded with respect to study treatment assignment, including all available supporting assessments (eg, EEGs, imaging studies, hospital reports). The external experts also identified additional information that would assist in the diagnosis of seizures. This information was requested from the Investigators and, when available, was provided to the external experts to complete their evaluation. The classification performed by the external experts concerning the likelihood of a diagnosis of seizures is provided in Table (7.5.2.2.2) 1. Of the 19 cases, 10 were identified as "likely," 4 as "possible," and 5 as "unlikely."

Table (7.5.2.2.2) 1 - Summary of expert panel assessment for the likelihood diagnosis of "seizures" - number of patients by likelihood

Expert Panel	Placebo	Placebo Run in	Rimonabant 5 mg	Rimonabant 20 mg	Total
Likely	3	2	2	3	10
Possible	1	0	0	3	4
Unlikely	2	0	0	3	5
Total	6	2	2	9	19

The incidence of seizures in clinical studies was compared between patients treated with placebo/off drug period and those treated with rimonabant. In order to properly reflect the different follow-up durations from study to study, all rates were calculated per patient-year. The patient-year exposure is calculated as the summation of the individual patients duration of treatment expressed in years. For the studies with re-randomization (RIO-North America and STRATUS-WW), the duration of treatment in each treatment period is taken into account in the corresponding arm of total patient-year exposure. The analyses took into account the placebo run-in period in the RIO studies: the patient-year exposure in placebo has been increased assuming that all the patients entering the run-in period were treated during 28 days with placebo.

The relative risk and its exact 2-sided 90% confidence limits were calculated under the assumption of a Poisson distribution using the mid-p method to ensure that the confidence limits provided the nominal coverage.

The relative risk of seizures based on patient-years has been estimated for all cases reported by the Investigators as seizures and reviewed by the external experts (n=19). Another analysis was based on the cases considered likely or possible seizures by the external experts (n=14). The 2 analyses are presented in Table (7.5.2.2.2) 2.

In the analysis taking into account the 19 cases, the observed relative risk of an event for rimonabant versus control was 0.68 [confidence interval 0.31, 1.5]. The analysis taking into account the 14 cases evaluated by the experts as likely or possible seizures showed similar results.

Table (7.5.2.2.2) 2 - Incidence rate of seizures in completed studies (unstratified analysis including placebo run-in)

Number of events / Extent of exposure in patient-years [(a)] (%)				**Relative Risk (90% confidence interval) Rimonabant vs Placebo**
	Rimonabant			
Placebo	**5 mg**	**20 mg**	**All doses**	
Analysis of the 19 cases identified in the completed studies				
8/3451 (0.232%)	2/3263 (0.061%)	9/3597 (0.250%)	11/6979 (0.158%)	0.6800 (0.3138, 1.5058)
Analysis of the 14 cases assessed as "likely/possible seizures" by the experts				
6/3451 (0.174%)	2/3263 (0.061%)	6/3597 (0.167%)	8/6979 (0.115%)	0.6593 (0.2665, 1.6771)

(a) Patient exposure includes placebo run-in periods and non controlled study periods

When reviewing the observed 19 cases of seizure, 8 were reported on placebo/off drug period and 11 during rimonabant treatment. No specific pattern of seizure characteristics has been identified in the rimonabant treated patients. When considering the 14 cases that were assessed as "possible," or "likely" seizures, 6 were reported with placebo, and 8 on rimonabant:

- In the 8 rimonabant cases, 1 case was reported in a crack abuser who attempted suicide using large doses of bupropion (a drug known to induce seizures) while in a rimonabant study for smoking cessation, 1 case was observed in a patient diagnosed with and surgically treated for meningioma. In 3 other cases, a previous history of seizures 10 years before (N=2) and of memory lapses evoking partial epilepsy (N=1) was documented, although the patients were not currently treated with anti-epileptic drugs. The 3 remaining cases had no underlying disease or identified alternative explanation.
- In the 6 placebo cases, 1 patient had a previous history of epilepsy not treated with an antiepileptic drug; 1 case was observed in a patient who had a medical history of astrocytoma treated with carbamazepine up to inclusion in the study. The four remaining cases had no known underlying disease or identified alternative explanation and one of these cases was observed in a patient 3 months post-placebo treatment.

Ongoing studies

For ongoing studies with rimonabant, the inclusion criteria have been relaxed to include patients with treated epilepsy.

In the ongoing program, 8 cases of seizures were reported by the Investigators and reviewed by the same external experts. Following this review, all cases were unblinded yielding: 2 cases in the placebo group and 4 cases in the rimonabant 20-mg group were assessed as likely or possible seizures. In addition, 2 cases in the rimonabant 20-mg group were evaluated as unlikely seizures by the experts.

The 4 possible/likely cases in the 20-mg group had a documented history of neurological disorder that could explain the event: 1 had a recent history of stroke (9 months before the seizure) and had hyponatremia (126 mmol/L), 1 had a history of phenytoin treatment for tremor and a history of stroke, 1 had a history of pituitary tumor and was treated for a myoclonic seizure, and 1 had a history of treated seizure disorder but was unable to take his anti-epileptic medication due to gastroenteritis. The 2 placebo cases occurred in a specific context: 1 patient had an accidental fall resulting in a head trauma, an intracranial hematoma, and a seizure, and 1 occurred in a patient with a medical history of surgery for cerebral abscess.

In conclusion, data from the ongoing studies with rimonabant do not provide new information as compared to the completed trials. However, as the number of cases remains low, sanofi-aventis has proposed the following labeling in the Package Insert:

- "Results from nonclinical studies suggest that rimonabant has a weak proconvulsant potential when administered to animals, which is not confirmed in the clinical situation. A comprehensive evaluation of the available clinical data has shown that

cases of seizures have been rarely reported in patients treated with ZIMULTI™ with no evidence of an increase in the seizure rate in patients treated with ZIMULTI™ 20-mg compared to placebo. ZIMULTI® has not been studied in patients being treated for epilepsy. ZIMULTI® should be used with caution in patients being treated for epilepsy."

7.5.2.3 Conclusions of neurological events

Dizziness, paresthesia, hypoesthesias, tremor, memory impairment, confusion, and disorientation all occurred in a small number of patients more frequently in the rimonabant 20-mg group than in the placebo group. The symptoms were generally mild and resolved quickly after withdrawal of the trial medication. No serious neurological AEs occurred that were related to rimonabant treatment. Newly diagnosed multiple sclerosis was seen in the placebo and rimonabant groups with equal frequency.

Rare cases of seizures were reported in all treatment groups, with similar frequency between rimonabant and placebo.

7.6 Other safety parameters

Standard laboratory tests did not provide any evidence of safety concerns with respect to the main biological functions (liver, renal, hematology, electrolytes, or metabolism). Similarly, the review of vital signs including supine BP and HR did not raise any safety concern.

In a thorough ECG study, rimonabant did not increase the QT/QTc interval at the therapeutic dose (20-mg) or at a supratherapeutic dose (60-mg) administered for 28 days. This absence of effect was confirmed by the database of ECGs recorded during the Phase 3 program and the absence of documentation of any AE that could be related to a cardiac arrhythmia.

8. SAFETY FROM POSTMARKETING SURVEILLANCE REPORTS

As of the cut-off date of this document, 01 March 2007, rimonabant has been approved in more than 30 countries in the European Union, America, and Asia, and was launched in 11 European countries, Argentina, Chile, and Mexico. The estimated worldwide postmarketing exposure, mainly in Germany and the UK, up to the cut-off date was 108 730 patients, and 1448 individual case safety reports (133 per 10 000 patients) were spontaneously reported to the Sponsor from this patient population:

- 721 cases were received from Healthcare Professionals, either directly (N=712) or through Regulatory Authorities (N=9), of which 136 were serious;
- 727 spontaneous cases were received from consumers of which 24 were serious.

No cases were received from partners or identified in the international literature.

It is noteworthy that 34% (495/1448) of the spontaneous cases were stimulated reports, initially received through phone calls issued by call centers dedicated to patients' support programs, mainly in the UK.

Nine percent (125/1448) of the individual case safety reports referred to serious and unlisted first main reactions, based on the core safety information for rimonabant created on 06 July 2006, and the most frequently reported SOCs of the first main reaction were psychiatric disorders (23%), GI disorders (22%), or nervous system disorders (15%); the most frequently reported adverse drug reactions were nausea/vomiting, depressed mood/depression, diarrhea, and dizziness.

Based on the safety specifications defined in the registration dossier and summarized in the risk management plan, and additionally based on the information included in the spontaneous reports received up to the cut-off date, the review of the postmarketing data focused on the following:

- Identified risks: depressive disorders (including suicidality-related reactions), anxiety, sleep disorders, dizziness, and neurological sensory disturbances of skin;
- Potential risks and signals: convulsions, aggression, and withdrawal syndrome.

8.1 Identified risks

Depressive disorders, including suicidality-related reactions

Depressive disorders, including suicidality-related reactions, were reported in 133 medically confirmed cases (reporting rate: 12.2/10 000 treated patients). Details of these cases include:

- 26% of cases were considered serious;
- The adverse reactions started during the first month in 99/133 cases;
- Depressive disorders were associated with particular psychiatric features or other psychiatric reactions in 31 cases: suicidality-related disorders (N=14), aggression/ aggressiveness (N=9), manic disorders, personality changes, hallucinations and/or behavior disorder (N=2, each), and paranoid symptoms and nervous breakdown (N=1, each);
- The 14 cases of suicidality-related disorders, 11% of the medically-confirmed cases, referred to suicidal ideation: depression was also mentioned in 11 of these cases and a context of hallucinations/psychotic disorder, anxiety and panic reaction were mentioned in 2 cases;
- 54 patients had a prior psychiatric history and/or suffered from psychiatric diseases.

Anxiety

Anxiety or anxiety-related symptoms were reported in 119 medically confirmed cases (reporting rate: 10.9/10 000 treated patients). Details of these cases include:

- 25% were considered serious;
- 25% were panic disorders;
- In 57% of the cases, other psychiatric reactions were also mentioned, ie, mostly depressive disorders, sleep disorders, and anger/aggression.

Sleep disorders

Sleep disorders were reported in 101 medically-confirmed cases (reporting rate: 9.3/10 000 treated patients). Details of these cases included:

- 36 were considered serious;
- Approximately 92% of the reported reactions were sleep disorder or insomnia (79%) and nightmares (13%). The remaining isolated cases referred mostly to parasomnia;
- In approximately 62% of the reports, other psychiatric reactions were also mentioned, ie, depressive disorders/mood disorders and/or anxiety/panic disorders.

Dizziness

Dizziness was reported in 68 medically-confirmed cases (reporting rate: 6.2/10 000 treated patients). Details of these cases include:

- 11 were serious;
- Vertigo (not otherwise specified [NOS]) or positional vertigo was specified in 4 cases;
- Dizziness was concomitantly reported with, or related to, other reactions in 56 of 68 cases, mostly digestive disorders and/or pain (mainly headache), blood pressure or blood glucose fluctuations, and headache and/or hyperhydrosis.

Neurological sensory disturbances of skin

Neurological sensory disturbances of the skin were reported in 48 medically confirmed cases (reporting rate: 4.4/10 000 treated patients). Details of these events include:

- 14 were considered serious;
- In almost 30% of the cases, paresthesia/hypoesthesia/pain in an extremity were reported in a specific neurological context, ie, cerebrovascular accident (presumably ischemic stroke) or trigeminal neuralgia, or were associated with other neurological disorders;
- In approximately 27% of the cases, paraesthesia, pain in an extremity, or sensory disturbance were associated with psychiatric disorders, mainly depressive symptoms, anxiety and panic attacks;
- Approximately 27% of the patients presented with diabetes mellitus.

8.2 Potential risks

Convulsions

Convulsions were reported in 2 medically confirmed cases (reporting rate: 0.2/10 000 treated patients) and included 1 case of delusion and convulsion and 1 case of nocturnal convulsions.

Withdrawal syndrome

Potential withdrawal syndrome was reported in 15 medically confirmed cases (reporting rate: 1.4/10 000 treated patients). The reported reactions were psychiatric reactions (euphoric mood, depression, anxiety, and sleep disorders), coronary artery disorders, cerebrovascular accident (presumably ischemic stroke), dizziness, asthma, pancreatitis, diverticulitis, gluteal pain, hematoma, and thrombocytopenia.

Aggression

Aggression was reported in 15 medically confirmed cases (reporting rate: 1.4/10 000 treated patients). Details of these cases include:

- 5 cases were considered to be serious;
- Reported reactions were aggressive behavior/reaction (N=7), aggressiveness/feeling aggressive (N=6), and aggression (NOS) (N=2);
- It is noteworthy that 2 patients had a history of depression and/or panic reaction, 1 patient suffering from Prader-Willi syndrome was treated with risperidone, and 3 patients were treated with antidepressants or benzodiazepines;
- In all cases except one, other psychiatric disorders were also mentioned, mostly depressive disorders and mood swings (N=10), anxiety or anxiety-related symptoms (N=3), and psychotic disorder (N=1).

8.2.1 Conclusions of postmarketing surveillance

No relevant additional information arose from the review of the potential or identified risks defined in the Risk Management Plan. No other reactions were identified from spontaneous reporting that would signal a new risk based on their frequency of reporting and/or the nature of the cases reported.

Safety data collected from worldwide sources during this reference period support the safety profile of rimonabant that was observed in clinical trials and presented in the registration file. No new relevant safety findings were identified that require additional safety actions, such as changes to the company reference document for rimonabant.

9. RISK MANAGEMENT PROGRAM

9.1 Overall principles

Based on the following safety specifications:

- Identified risks: depressive disorders (including the potential for suicidality-related events), anxiety, sleep disorders, sensory changes (dizziness, neurological sensory disturbance of skin);
- Potential risks: convulsions, withdrawal syndrome;
- Effects in the following populations or conditions where collected safety information is currently insufficient to reach scientific conclusions: children under the age of 18, elderly patients over the age of 75, pregnancy, lactation, African-Americans and Asiatic patients, patients with hepatic impairment or renal impairment, concomitant use of antidepressants and potent CYP 3A4 inhibitors; and
- Potential risk of uses of the drug inconsistent with product labeling in patients with diseases, conditions or concomitant therapy that raise identified or potential safety concerns. In addition, since obesity is a chronic disorder, short-term use is not recommended and the company does not intend to promote the product for short term cosmetic use.

Sanofi-aventis has implemented a pharmacovigilance plan, to monitor the safety profile of rimonabant after product launch that comprises activities beyond routine pharmacovigilance practices. These additional activities consist of:

- Use of specific report forms to collect detailed information on depression, neurological AEs, and convulsion on spontaneously reported observations;
- Evaluation of the background incidence rates of important risks in the target population, using The Health Information Network (THIN), Atherosclerosis Risk In Communities (ARIC) and KPNW databases;
- After launch, evaluation of the potential association between rimonabant use and potential or identified risks using the THIN and LabRx databases, and prescription event monitoring, (as already conducted in the UK);
- Continued assessment of safety and efficacy in life cycle management clinical trials.

Sanofi-aventis is aware of the possibility of uses of the drug inconsistent with product labeling in patients with diseases, conditions, or concomitant therapy that raise identified or potential safety concerns. In addition, since obesity is a chronic disorder, short-term use is not recommended, and the company does not intend to promote the product for short term cosmetic use and is committed to educational and communications outreach activities in an effort to promote use consistent with product labeling and minimization of the identified and potential risks. Risk minimization activities include a comprehensive set of concerted and consistent activities to communicate data regarding use of the drug consistent with product labeling and patient populations, including educational, communication, and promotional activities, as described hereunder:

- Educate healthcare professionals on the use of rimonabant in abdominally obese patients with other co-morbidities such as type 2 diabetes mellitus or dyslipidemia and on the overall safety and discouraging use in patients with diseases, conditions, or concomitant therapy that raise identified or potential safety concerns. In addition, since obesity is a chronic disorder, short-term use is not recommended and the company does not intend to promote the product for short-term cosmetic use.
- Provide patients with educational material to promote a better understanding of cardiovascular and metabolic risks factors, particularly in the context of abdominal obesity, in a way they can understand to favor long-term medical rather than short-term cosmetic use.
- Offer physicians simple ways to educate patients on the clinical benefits of long-term therapy for appropriate patient types while setting treatment expectations.
- Provide physicians and other healthcare professionals with regular educational support tools that they can use as appropriate to assist their patients in efforts to reach the goal they have established for them.
- Integrate responsible and practical diet and exercise information and programs in a supportive, accessible manner for health care professionals and their patients for when they prescribe rimonabant.
- Monitor media publications to assess messages that could potentially encourage use of the drug in patients with diseases, conditions or concomitant therapy that raise identified or potential safety concerns. In addition, since obesity is a chronic disorder, short-term use is not recommended and the company does not intend to promote the product for short-term cosmetic use.
- Implement specific training of sanofi-aventis representatives in order to provide health care professionals with the appropriate information on the correct and inappropriate use of the drug according to labeling.

A specific internal process has been set up to ensure a seamless implementation of these initiatives across affiliates. This process includes the tracking of the implementation and impact of each of these activities.

The effectiveness of the risk minimization plan is being evaluated locally and on an overall basis by the measure of the use of the drug in patients with diseases, conditions, or concomitant therapy that raise identified or potential safety concerns. In addition, since obesity is a chronic disorder, short-term use is not recommended and the company does not intend to promote the product for short-term cosmetic use through the monitoring of prescriptions mentioned above. This is done by evaluation through market research analysis, conducted by an independent third party, in which a number of physicians randomly selected so as to be representative of the population of physicians in a given country are interviewed to assess brand usage as compared to labeling specifications and to make decisions on follow-up corrective actions, if deemed warranted consistent with the goals of the risk minimization plan.

This methodology of an ad hoc survey has been chosen, as opposed to collecting data from existing databases, to obtain more timely information than databases which do not cover specialists and require more time to provide sufficient patient exposure data. A retrospective design was considered the most appropriate to collect information rapidly and to avoid influencing the physician's prescription. The major limitation of this retrospective design is recognized, namely the possibility for the physician to provide his/her "best" patients records. This possibility is expected to be minimal for the first waves of the prescription survey, when physicians have fewer patients to describe. Later on, it would be possible to reduce this phenomenon by asking physicians to report all records of prescriptions made on a single day. The results will be compared to the data obtained with other sources of information that will become available, such as the observational databases collected in computerized physician practices, when enough patients are recorded.

9.2 EU Experience

The above-mentioned RMP principles were submitted in the first European RMP (EU-RMP) dated 22 June 2006 and agreed upon by the EMEA, with the addition of 2 potential risks that the Agency requested to be considered in the safety specifications: sexual dysfunction/effects on libido and hepatic toxicity.

On 18 February 2007, the EU-RMP has been updated to version 2 with the same data lock date as the first 6-month PSUR. This Version 2 has been written in compliance with the format of the "Template for EU Risk Management Plan," Annex C to the EMEA "Guideline on Risk Management Systems for Medicinal Products for Human Use" (EMEA/CHMP/96268/2005), in effect since 27 September 2006 (EMEA/192632/2006).

The safety specifications were updated with the following data:

- Five (5) completed clinical trials, whose data have been integrated with those of Phase 3 clinical studies from the original dossier. This global new pooling of data from the 2 main programs (obesity and smoking cessation) has been used to update the exposure section and the estimates of frequency of identified and potential risks;
- Spontaneous AE reports in the countries that had launched rimonabant during the 6-month period covered and analyzed in the first PSUR;
- Epidemiology results presenting background incidence rates of seizure in the THIN database that will be used to study the association between seizures and rimonabant use in the UK. Incidence rates in the obese population and in the overweight population with comorbid conditions were not significantly different from that in normal weight patients. It was concluded that there was no new safety concern, and the list of identified and potential risks was maintained unchanged.

The pharmacovigilance plan has been updated to note the completion of the above-mentioned clinical and epidemiological studies, and to add a new prescription-event monitoring (PEM) study in the UK, as this methodology has been used for years in this country to evaluate the safety of any new medicine soon after launch.

To measure the overall effectiveness of the minimization plan, results from a prescription survey covering the first months of experience in the UK (August to November 2006), the first country to launch, were available. At that time, it was estimated, from sales data, that 15 980 patients had received rimonabant in post-marketing conditions.

It was concluded that the risk minimization plan required no adjustment, as its first measure of effectiveness in the UK showed an acceptable level of off-label use based on the results of the prescription survey.

Preliminary results available from other European countries having launched rimonabant provide very similar results. Therefore, the European experience so far indicates that the drug is used in accordance with labeling in more than 95% of the cases, which is indicative of the Company's approach to educational, communication, and promotional activities having encouraged appropriate use of the drug consistent with labeling specifications, once on the market.

9.3 US proposal

Like Europe and the rest of the world, the main objective of the US Risk MAP is to reduce the possibility of use of the drug inconsistent with product labeling in patients with diseases, conditions, or concomitant therapy that raise identified or potential safety concerns. In addition, since obesity is a chronic disorder, short term use is not recommended and the company does not intend to promote the product for short term cosmetic use. This will be done by increasing the knowledge of key stakeholders (including prescribers/health care professionals, pharmacists, and patients) on the safety and efficacy profile of rimonabant.

Therefore, the overall strategy is to accomplish risk minimization through a Targeted Education and Outreach Program and a Reminder System using some of the tools described below. The overall RiskMAP effectiveness will be assessed periodically and further ongoing and iterative development is expected with follow-up actions implemented, as needed. The company is currently considering alternatives to obtain input from healthcare participants (eg, physicians, pharmacists, etc) as part of the ongoing process of evaluating the effectiveness of the RiskMAP.

Targeted Education and Outreach Program tools

The Targeted Education and Outreach program will be based on the coordinated implementation of tools developed to cover 3 main domains, ie, medical education, communication, and promotion. This will be reinforced by the use of 2 additional tools, ie, a physician checklist and a Medication Guide.

1. Medical education

   CME programs

   Educational grants supported by sanofi-aventis Medical Affairs are selected based on factors including educational needs, scientific and medical relevance, educational design, and compliance with standards set-forth by the Accreditation Council for Continuing Medical Education (ACCME) and other regulatory bodies. Ultimately, CME providers must independently validate educational needs and select the learning objectives and specific content for any sanofi-aventis Medical Affairs supported program. CME educational strategy will be fulfilled by the implementation of the following guidelines:

   - Educational grants in the area of obesity associated with the comorbidities of type 2 diabetes or dyslipidemia:
     - In response to unsolicited written requests (including those from grant recipients), sanofi-aventis Medical Affairs will provide information on the safety profile of rimonabant and the conditions of use to portray a balanced view of therapeutic options;
     - All medical education providers will be provided information on the safety profile of rimonabant when appropriate;
     - Programs in this area will be directed at the populations of health care providers likely to provide treatment for the abdominally obese patient with the comorbidities such as cardiologists, endocrinologists, psychiatrists, primary care physicians, pharmacists, nurse practitioners, physician assistants, and nurses.

Non-CME programs (Promotional Speaker Programs)

Sanofi-aventis will implement an integrated educational program for prescribers/health care professionals, pharmacists, and patients regarding the risks and benefits associated with the use of rimonabant. Points of emphasis will contain reinforcement of uses consistent with the US label and identification of uses or patient populations that raise identified or potential safety concerns. Specific tools will be developed:

- Educational slide kit, which outlines patient populations as well as risk-benefit information;
- Participant questionnaire;
- Handouts to reinforce messages.

Consumer educational materials

- A variety of educational materials will be made available to patients including:
  - Patient starter kit with educational materials;
  - Online education that allows patients to scan educational materials on the risk/benefit profile of rimonabant;
  - Unbranded educational materials for patients;
  - Medication Guide delivered by the Pharmacy at the time of fulfillment of prescriptions, including the first and refill prescriptions.

2. Communication

Sanofi-aventis will implement a communication plan to inform US journalists about rimonabant and the underlying diseases and conditions for which it is used consistent with the product labeling. The plan will consist of the following:

- Providing information regarding labeled uses and patient populations for rimonabant. These “right patient” messages will be incorporated as appropriate into company press releases, backgrounders, fact sheets, Q&As, visuals such as b-roll, etc, to be developed and distributed to the media for their reference and use in coverage.
- Conducting outreach to US journalists, including top-tier journalists at national media and consumer magazines, health web sites and trade publications, to further their understanding about the growing issue of obesity and its associated risk factors in the US, rimonabant and its novel mechanism of action, and other information regarding the risk-benefit profile of rimonabant consistent with the product labeling. Education will include individual briefings with reporters, consumer and trade media briefings/roundtables, interviews, and press material distribution.
- Outreach efforts in response to requests from advocacy/patient groups who seek information on rimonabant for their membership.
- Upon request, sanofi-aventis will conduct label review sessions with prescribers/health care professional who discuss rimonabant with the US media, to ensure the risks and benefits of rimonabant are clearly communicated.

- A press room will be created on the sanofi-aventis web site to provide US journalists with easily accessible, accurate information about rimonabant, its appropriate use, and patient education materials. The company will post appropriate product information, FAQs, press materials (eg, releases, backgrounders, etc) on the press room and commits to updating the site as new information (eg, data) becomes available. As needed, the company will use a variety of communications vehicles (eg, media interviews, patient brochure, local market seminars, take-one pamphlets in physician waiting rooms, etc) to educate journalists and the public on the risks and benefits of rimonabant. Initiative materials will be submitted to DDMAC for review and approval and the company commits to making modifications if/as requested by DDMAC.

3. Promotion

   Promotional materials and activities will include, but will not be limited to the following:

   - Patient populations and uses consistent with product labeling leave-behind:
     - This piece would list on one side information on uses consistent with the final product labeling and underlying diseases and conditions;
     - Side 2 of the piece would focus on inappropriate patients, eg, warnings and precautions or recommendations for use with caution, as outlined in the physicians checklist.
   - Sales professionals:
     - Sales professionals for rimonabant will be trained and certified on their ability to correctly and effectively communicate to healthcare providers information relating to appropriate uses and risk information;
     - Sales professionals will present information consistent with the product labeling as agreed upon with FDA, and all promotional materials used at launch with healthcare professionals will be subject to prior approval with the FDA and the Division of Drug Marketing and Advertising (DDMAC);
     - Post-launch research will be conducted to assess physician understanding of risk- benefit as well as appropriate use in patients.
   - If market research indicates a lack of understanding by prescribers, follow-up actions will be discussed and implemented as part of the RiskMAP.

4. Direct-to-consumer advertising

   Sanofi-aventis is committed to educating healthcare professionals regarding new medications before starting any direct-to-consumer (DTC) advertising (ie, advertising time or space purchased for the purpose of presenting information on one or more sanofi-aventis prescription drug products to consumers). Sanofi-aventis will withhold DTC advertising for rimonabant for the period of at least 6 months after commercial launch. This exclusion does not apply to time or space purchased to raise awareness of or educate consumers about diseases/conditions or to provide educational materials as discussed above in consumer educational materials.

5. Physician Check list:
   Sanofi-aventis will prepare and distribute a physician's checklist to provide readily available information for healthcare professionals to consider in making prescribing decisions for individual patients. This checklist will be based on the product labeling and will be developed with the FDA after finalization of the prescribing information.

6. Medication Guide:
   A medication guide will be provided to pharmacists for distribution to patients filling rimonabant prescriptions. It will summarize important identified and potential risks of which patients should be aware, and will instruct patients to report to their healthcare professionals any relevant medical history, concomitant medications, and other information that could help prevent serious adverse effects. This instrument will be fully developed with the FDA after finalization of the prescribing information.

   Reminder System tools
   To enhance the effectiveness of the targeted education and outreach program, the following reminder system tools are proposed:
   - To periodically evaluate the effectiveness of company educational programs, a third-party vendor with expertise in evaluating outcomes will be hired to develop appropriate methodology (including matched controls) such as case-vignettes. This technique will be used to assess if educational program participants understood the safety data.
   - A patient journey to be used by both patients and physicians alike: This program would inform physicians and patients of the benefits and risks associated with rimonabant use over time. For physicians, one alternative under consideration is a recommendation to assess patients after 3 months of therapy for current results, counseling on diet and exercise, and ongoing expectations, and evaluation of potential side effects early on in therapy.
   - Rimonabant appropriate-use program: A launch program to educate physicians and their allied health professionals on uses consistent with labeling, expectations for therapeutic response, and assessment of side-effect profile.

   The effectiveness of the US-RMP will be regularly measured with the following prescription monitoring tools:
   - Prescription survey will consist of quantitative primary research, undertaken with sample sizes robust enough to enable country projections, through questionnaires to physicians based on collected patient cases. Monitored on a quarterly basis, this can provide sequential information on the types of patients to whom the drug is prescribed (BMI, waist circumference, presence/absence of cardiovascular and other co-morbidities (including severe depression, co-treatments [including antidepressants], intended duration of treatment).

- Secondary prescription data tracking will consist of quarterly analyses of the prescriptions filled in at pharmacy level. These ongoing monitoring of prescribing practices will be complemented and validated by the correlation with the measure of the incidence rates of outcomes of interest (such as seizures, depression, suicides) in automated health care databases (such as LabRx®) as soon as they will provide sufficient quantity of data.

The overall RiskMAP effectiveness will be assessed periodically, and further ongoing and iterative development is expected with follow-up actions implemented, as needed. The company is currently considering alternatives to obtain input from healthcare participants (eg, physicians, pharmacists, etc.) as part of the ongoing process of evaluating the effectiveness of the RiskMAP.

10. BENEFIT AND RISK

10.1 Treatment of obese and overweight patients

The safety and efficacy of rimonabant were demonstrated in 4 adequate and well-controlled studies with reproducible results, and sustained over time, up to 1 year (in all 4 studies) and 2 years (in 2 studies). The 20-mg dose of rimonabant had favorable metabolic effects including improved insulin sensitivity, increased HDL-C, and decreased TG, and improved glucose control in type 2 diabetes above and beyond its effect on body weight loss (about 8 kg from baseline and 10 kg from screening). Based on this body of data, rimonabant, used in conjunction with a reduced calorie diet and physical exercise, will be an important option in the management of obese and overweight patients with associated cardiovascular risk.

Body weight management

Despite all efforts from the medical community and patients to fight the obesity epidemic using diet, counseling, and approved and non-approved drugs, there is still an unmet medical need for pharmacotherapy that can help to achieve clinically significant body weight loss and prevent short term relapse.

Clinically meaningful mean body weight loss, confirmed by the 2- to 3-fold higher rate of 5% and 10% responders compared with diet alone observed after 1 year, demonstrates that 20-mg rimonabant results in sustained body weight loss and waist circumference reduction.

As expected for this chronic disease, when treatment was discontinued after 1 year, body weight regain occurred. In contrast the body weight loss was maintained when rimonabant was continued up to 2 years. This reduction in the risk of body weight regain is of importance in a chronic disease where most therapeutic means fail in the long term.

Severe obesity (BMI ≥40.0 kg/m²) is increasing much faster than obesity, leading to more and more bariatric surgery and its related morbidity/mortality. The RIO program reflects

the increased incidence of severe obesity with approximately 30% of patients with BMI ≥40 kg/m² in the 2 studies where severely obese patients were allowed to participate (representing more than 1300 patients). Rimonabant 20-mg almost halved the percentage of patients with severe obesity after 1 year of treatment. One patient out of 4 lost more than 10% of his/her baseline body weight, tripling the effect of the diet. In severely obese patients, rimonabant demonstrated improvements in lipids and glucose/insulin homeostasis similar to the improvements seen in nonseverely obese patients.

Type 2 diabetes

Both the AHA and ADA emphasize the importance of obesity in diabetes in risk factor management. Thus, there is a need for treatment of diabetic patients that will not only lower HbA_{1c}, but also decrease body weight and the metabolic disorders associated with excess weight. The RIO-Diabetes study in patients with type 2 diabetes showed that rimonabant at the dose of 20-mg once daily could accomplish these goals, when diet plus the single agent (metformin or sulfonylureas) did not result in adequate glycemic control. The 0.7% decrease in HbA_{1c} over the placebo effect, with 67.9% of patients reaching a HbA_{1c} level <7%, demonstrated a clinically significant improvement in glucose control.

The 6-month SERENADE study in treatment-naive type 2 diabetic patients confirmed the benefits seen with rimonabant in the 12-month RIO Diabetes study. The SERENADE study showed a placebo-adjusted decrease in HbA_{1c} of 0.5% in the overall population and a 1.2% decrease in patients with a baseline HbA_{1c} above 8.5%. About half of the benefit was beyond what was expected from weight loss alone. Moreover, the 4.0 kg placebo-adjusted weight loss and the 3.7 cm decrease in waist circumference points toward a reduction in cardiovascular risk.

Safety

The safety profile of rimonabant was assessed in a large database comprising the obesity, diabetes, and smoking cessation programs involving more than 16 000 individuals, of whom 12 836 were treated with rimonabant, contributing more than 3400 patient-years of experience at the 20-mg dose, 7447 with 20-mg once daily for up to 6 months/2 years [Table (1.7) 1].

A similar safety profile was observed between the obesity and diabetes populations. The GI disorders that were reported more frequently with rimonabant than placebo were generally mild and transient, rarely led to treatment discontinuation, and were not related to body weight loss. Such events should not have an impact on patient compliance during chronic administration or, at most, should be considered a tolerability issue and not as a safety concern.

A greater incidence of dizziness, anxiety, depressed mood, and depressive disorders was observed in the 20-mg rimonabant group, compared with the placebo group. Most of these cases were mild and transient. There were few cases of MDDs and no increase in suicides, although there was an increase in suicidal ideation with rimonabant 20-mg. Increased rates of psychiatric events, including depression, have been reported with

currently approved weight loss agents and are described in their respective package inserts: orlistat (Xenical) (depression: 3.4% versus 2.5% at Year 2) and sibutramine (Meridia) (depression: 4.3% versus 2.5%, and emotional liability: 1.3% versus 0.6%) for active drug versus placebo, respectively.

In type 2 diabetes, rimonabant was well tolerated, with a somewhat greater incidence of paresthesia and muscle spasm. Importantly, there was a low risk of hypoglycemia, a finding of particular interest for use in patients already on drugs that have such adverse reactions. There was no evidence of an interaction with oral anti-diabetic drugs (metformin or sulfonylureas) in the RIO-diabetes study.

There was no particular safety issue related to long term use of rimonabant and there were no specific adverse reactions in those who discontinued the drug after several weeks or months of continuous use.

There was no identified area of concern on hematological, hepatic, or renal safety when rimonabant was used for up to 2 years. The drug was well-tolerated in the population of elderly patients randomized in this program, which had slightly higher exposure than younger patients.

Results from a thorough ECG study also demonstrated no increases in the QT/QTc interval at the therapeutic (20-mg) and at a supratherapeutic dose (60-mg) administered for 28 days. These results reiterate that rimonabant is not associated with any significant cardiac risk to the patient who would also benefit from the improvement in the cardiovascular risk factors.

Rimonabant at the dose of 20-mg demonstrated no clinically relevant interaction with other drugs, either in specific clinical pharmacology studies (ketoconazole, midazolam, Warfarin, orlistat (Xenical), oral contraceptives, digoxin, famciclovir, nicotine patches) or in the Phase 3 program. In patients taking statins or antihypertensive drugs (drugs that are expected to be frequently prescribed in this population) during the RIO studies, there was no significant increase in exposure to rimonabant and the safety profile was similar to that observed in the whole population. No difference in exposure to rimonabant was observed with the most common drugs prescribed in the RIO patients. Rimonabant can be taken with or without food, preferably in the morning.

In conclusion, the benefit risk ratio of rimonabant at the dose of 20-mg once daily is favorable in the obese, overweight, and diabetes populations. By working to normalize a dysfunctional endocannabinoid system, rimonabant addresses the root causes of the disease, ie, abdominal obesity and insulin resistance.

In particular, for patients with type 2 diabetes, the benefit risk ratio is particularly favorable; rimonabant improves glucose control, decreases body weight, and improves the lipid profile in a situation of inadequate glucose control with oral antidiabetic drugs that generally further increase body weight and fail to control the dyslipidemia of diabetes.

The overall benefits on body weight, waist circumference, and metabolic parameters seen in all patient populations studied clearly outweigh the defined risks that are manageable in clinical practice.

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