SYNOPSIS

Title of the study:	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 (EFC5826)
Investigator:	[redacted]
Study centers:	The study was conducted at 976 centers in 44 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Portugal, Romania, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, United Kingdom, United States of America).
Publications (reference):	None
Study period:	
Date first patient enrolled:	22 December 2005
Date last patient completed:	29 April 2009
Phase of development:	3
Objectives:	The objectives of the protocol were as follows: ***Primary objective***: To demonstrate the efficacy of rimonabant versus placebo for reducing the risk of myocardial infarction (MI), stroke, or cardiovascular death in patients with abdominal obesity at increased risk for such cardiovascular events. ***Secondary objective***: To demonstrate the efficacy of rimonabant versus placebo for reducing the risk of MI, stroke, cardiovascular death, or hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure) in patients with abdominal obesity at increased risk for such cardiovascular events. ***Other objectives***: To demonstrate the effect of rimonabant versus placebo on all-cause mortality. To assess the safety of rimonabant in the study population over the duration of the study. The study was discontinued prematurely after all patients had been randomized (18 695 patients) due to the Sponsor's decision to discontinue the rimonabant development program. The monitoring, therefore, focused on the safety profile, based on the reporting of adverse events, and on the primary efficacy criterion. As a result, the analysis (as defined in the statistical analysis plan) only focused on these data and the results are presented through a synopsis-style report. The appendices attached to this synopsis-style report were chosen to provide the relevant information.
Methodology:	This was a long-term, multicenter, multinational, randomized, double-blind, placebo-controlled, 2-arm parallel group (rimonabant 20 mg once daily [OD] versus placebo) trial, stratified by study center.
Number of patients:	Planned: 17 000 Randomized: 18 695 Treated: 18 671
Evaluated:	Efficacy (intent-to-treat [ITT]) : 18 695 Safety (randomized and exposed patients): 18 671

Diagnosis and criteria for inclusion: Patients ≥55 years of age with abdominal obesity (waist circumference >88 cm [35 inches] in women or >102 cm [40 inches] in men), and at least 1 coronary heart disease risk equivalent or 2 major cardiovascular risk factors.

Coronary heart disease risk equivalents:

- Recent (within the past 3 years) documented MI.
- Stable angina with documented multivessel coronary disease, and/or history of multivessel percutaneous coronary intervention or multivessel coronary artery bypass graft surgery
- Recent (within the past 3 years) ischemic cerebrovascular episode. Computed tomography or magnetic resonance imaging must have been performed to document whether a lesion is associated with the ischemic episode and to rule out non-ischemic neurological disease.
- Documented symptomatic peripheral arterial disease (one of the following primary criteria must be satisfied):
  - current intermittent claudication (World Health Organisation [WHO] criteria),TOGETHER WITH ankle-brachial index (ABI) equal to or less than 0.85 in either leg at rest, or
  - history of intermittent claudication (WHO criteria) TOGETHER WITH either previous intervention by amputation, or reconstructive vascular surgery, or angioplasty in one or both legs because of atherosclerotic disease.

Major cardiovascular risk factors:

- Type 2 diabetes mellitus (fasting plasma or serum glucose equal to or greater than 126 mg/dL [7.0 mmol/L] on 2 or more occasions)
- Metabolic syndrome, as diagnosed by the presence of at least 2 of the following risk factors (if 3 of the risk factors listed below are fulfilled, this is equivalent to 2 major risk factors and the patient is eligible):
  - Elevated fasting triglyceride level
  - Low high density lipoprotein-cholesterol level
  - Impaired fasting plasma or serum glucose
  - Elevated blood pressure at baseline visit
- Asymptomatic cerebrovascular disease, with greater than 50% stenosis of a carotid, intracranial, and/or vertebral artery, or plaque on intima-media thickness, or revascularization
- Renal artery disease, with greater than 60% stenosis of a renal artery or revascularization
- Previous history of abdominal aortic aneurysm repair
- Asymptomatic ABI less than 0.85
- Elevated high sensitivity C-reactive protein greater than 3 mg/L
- Elevated age of 65 years or greater for males and 70 years or greater for females

Investigational product: SR141716 (rimonabant)

Dose: 20 mg tablet of rimonabant, OD

Administration: Oral

Batch numbers: [redacted]

Duration of treatment: 33 to 50 months

Duration of observation: 36 to 53 months

Reference therapy: Placebo

Dose: Matched to rimonabant, OD

Administration: Oral

Batch numbers: [redacted]

Criteria for evaluation:

Efficacy:

The primary efficacy criterion was the first occurrence of any component of the following cluster over the duration of study (randomization to study end date inclusive), as adjudicated by the Clinical Events Committee:

- Any MI (nonfatal or fatal),
- Any stroke (nonfatal or fatal),
- Cardiovascular death.

The secondary efficacy criterion was the first occurrence of any component of the following cluster over the duration of study (randomization to study end date inclusive):

- Any MI (nonfatal or fatal),
- Any stroke (nonfatal or fatal),
- Cardiovascular death, and
- Hospitalization for cardiovascular cause (unstable angina, transient ischemic attack, cardiac rhythm disorder, congestive heart failure, syncope, or urgent revascularization procedure).

Other criteria included all-cause mortality, and the following events taken separately:

- Any MI (nonfatal or fatal).
- Any stroke (nonfatal or fatal/ischemic, hemorrhagic or of uncertain type).
- Cardiovascular death.

Safety: Only adverse events were reviewed and described.

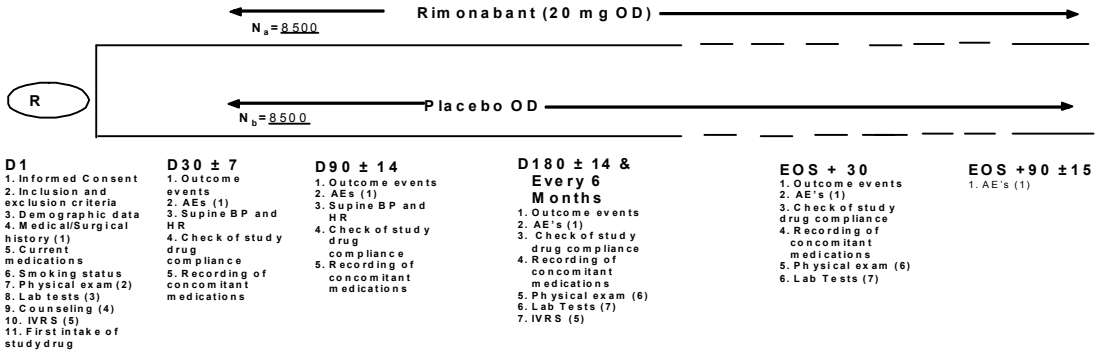
Statistical methods: Due to the premature discontinuation of the study, the common study end date was substantially earlier than planned and, therefore, the statistical power was considerably reduced. The analyses were focused on patient disposition, demographic characteristics, extent of exposure, the main efficacy analysis of the primary endpoint and all-cause mortality, and treatment-emergent adverse events (TEAEs).

Efficacy: The analyses were performed using the ITT population. For the primary analysis, all adjudicated events occurring from randomization to the study end date (inclusive) were counted, including events occurring after early permanent discontinuation of study drug. A time to event survival analysis approach was used for the primary endpoint analysis. The time from randomization to the occurrence of any event of the composite endpoint was compared between the 2 treatment groups using a 2-sided Log-rank asymptotic test. Statistical significance was to be claimed if the computed p-value is equal to or less than 0.05. Cumulative event rate for each treatment group was calculated using the Kaplan-Meier method and plotted over time. A Cox proportional hazards model with factor of treatment was used to calculate the relative risk estimate and the corresponding 95% confidence interval (CI).

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1 and summarized by treatment group using descriptive statistics.

Summary:

A summary of the study design is provided below and a study flowchart is provided at the end of the document.



1. Including revised specific neurological and psychiatric assessment, including C-SSRS
2. Body weight, waist circumference, height measurement, supine HR and BP, revised detailed neurological exam
3. Pregnancy test (women of childbearing potential), 12-lead ECG, hematology (Hb, Ht, WBC-diff, platelets), biochemistry (ALT, AST, ALP, creatinine)
4. Diet, exercise and smoking cessation.
5. IVRS call for treatment kit number; delivery of corresponding pack of study drug for 6 months treatment
6. Including body weight, waist circumference, supine BP and HR
7. Hematology (Hb, Ht, WBC-diff, platelets), biochemistry (ALT, AST, ALP, creatinine),

Summary of populations:

Table 1 summarizes the populations used in the efficacy and safety analyses.

Table 1 - Summary of patient populations – n (%) - randomized population

	Placebo	Rimonabant 20 mg	Overall
Randomized population	9314 (100%)	9381 (100%)	18695 (100%)
ITT Population	9314 (100%)	9381 (100%)	18695 (100%)
Randomized and exposed population	9302 (99.9%)	9369 (99.9%)	18671 (99.9%)

Note: % calculated using the number of randomized patients as denominator.

Patient disposition:

A total of 18 671 patients were exposed to the investigational product. Twelve patients in each treatment group were randomized but not exposed. A small percentage of patients, those who died during the study treatment period, were considered to have completed the study as planned. Most patients discontinued treatment as a result of the premature discontinuation of the study and were counted in the category "other reason". Approximately twice as many patients in the rimonabant group discontinued treatment due to an adverse event compared to those receiving placebo. Table 2 summarizes patient disposition including reasons for treatment discontinuation.

Table 2 - Summary of patient disposition – end-of-treatment – n (%) - randomized population

	Placebo (N=9314)	Rimonabant 20 mg (N=9381)
Patients randomized	9314 (100%)	9381 (100%)
Randomized but not treated	12 (0.1%)	12 (0.1%)
Randomized and treated	9302 (99.9%)	9369 (99.9%)
Completed study treatment period	179 (1.9%)	162 (1.7%)
Did not completed the study treatment period	9123 (97.9%)	9207 (98.1%)
Main reason for treatment discontinuation		
Adverse event	836 (9.0%)	1760 (18.8%)
Subject's request	555 (6.0%)	524 (5.6%)
Other reason	7624 (81.9%)	6816 (72.7%)
Missing	108 (1.2%)	107 (1.1%)

Note: % calculated using the number of randomized patients as denominator.
Missing: The reason for permanent treatment discontinuation was not entered into the database because either the Investigator did not complete the end of treatment page or the end of treatment page was not collected.
Note: All patients who have been reported as completing the study period were patients who died during the study period; however, some deceased patients were reported as not having completed the study.

Exposure:

The safety population in this study included 18 671 patients randomized and exposed to the investigational product, regardless of the amount of treatment administered. The median number of months the patients were exposed to the investigational products was higher in the placebo group (14.19 months) than in the 20 mg rimonabant group (12.25 months). Patient exposure, based on the safety population, is presented in Table 3.

Table 3 - Summary of exposure to study drug – randomized and exposed population

	Placebo (N=9302)	Rimonabant 20 mg (N=9369)
Cumulative exposure (patient years)	11708.0	10799.5
Extent of exposure (months)		
Number	9302	9369
Mean (SD)	15.10 (9.05)	13.83 (9.39)
Median	14.19	12.25
Min : Max	0.0 : 34.8	0.0 : 34.5
Count of patients [n(%)]		
< 6 months	2024 (21.8%)	2708 (28.9%)
[6-12[months	1994 (21.4%)	1887 (20.1%)
[12-18[months	1526 (16.4%)	1405 (15.0%)
[18-24[months	1683 (18.1%)	1470 (15.7%)
[24-30[months	1739 (18.7%)	1610 (17.2%)
≥ 30 months	336 (3.6%)	289 (3.1%)

Demographics:

Patient demographic characteristics are presented in Table 4.

Table 4 - Summary of patient demographics at baseline - ITT population

	Placebo (N=9314)	Rimonabant 20 mg (N=9381)	Overall (N=18695)
Gender [n (%)]			
Number	9314	9380	18694
Male	5923 (63.6%)	6036 (64.3%)	11959 (64.0%)
Female	3391 (36.4%)	3344 (35.7%)	6735 (36.0%)
Race [n (%)]			
Number	9313	9380	18693
Caucasian	7858 (84.4%)	7894 (84.2%)	15752 (84.3%)
Black	218 (2.3%)	244 (2.6%)	462 (2.5%)
Asian / Oriental	791 (8.5%)	793 (8.5%)	1584 (8.5%)
Other	446 (4.8%)	449 (4.8%)	895 (4.8%)

Ethnicity in US			
Number	2691	2703	5394
American Hispanic	96 (3.6%)	86 (3.2%)	182 (3.4%)
American non Hispanic	2595 (96.4%)	2617 (96.8%)	5212 (96.6%)
Age (years)			
Number	9314	9380	18694
Mean (SD)	64.9 (6.8)	64.8 (6.8)	64.9 (6.8)
Median	64.0	64.0	64.0
Min : Max	53 : 88	47 : 93	47 : 93
<65	4788 (51.4%)	4912 (52.4%)	9700 (51.9%)
[65-75[	3610 (38.8%)	3558 (37.9%)	7168 (38.3%)
≥ 75	916 (9.8%)	910 (9.7%)	1826 (9.8%)
Smoking status			
Number	9312	9377	18689
Never	3423 (36.8%)	3523 (37.6%)	6946 (37.2%)
Current	1074 (11.5%)	1094 (11.7%)	2168 (11.6%)
Former	4815 (51.7%)	4760 (50.8%)	9575 (51.2%)
Height (cm)			
Number	9311	9374	18685
Mean (SD)	168.16 (10.05)	168.35 (10.11)	168.26 (10.08)
Median	169.00	169.00	169.00
Min : Max	121.0 : 208.0	117.0 : 205.0	117.0 : 208.0
Weight (kg)			
Number	9310	9376	18686
Mean (SD)	96.96 (19.63)	96.96 (19.56)	96.96 (19.60)
Median	94.80	94.50	94.60
Min : Max	45.0 : 241.5	50.0 : 231.8	45.0 : 241.5
Waist circumference (cm)			
Number	9310	9376	18686
Mean (SD)	114.87 (12.75)	114.82 (12.77)	114.84 (12.76)
Median	113.00	112.67	113.00
Min : Max	88.3 : 226.3	88.3 : 222.7	88.3 : 226.3
For men			
≤ 102 cm	10 (0.2%)	8 (0.1%)	18 (0.2%)
> 102 cm	5913 (99.8%)	6028 (99.9%)	11941 (99.8%)

For women			
≤ 88 cm	0	0	0
> 88 cm	3391 (100%)	3344 (100%)	6735 (100%)
BMI (kg/m^2)			
Number	9308	9372	18680
Mean (SD)	34.20 (5.84)	34.14 (5.88)	34.17 (5.86)
Median	33.17	33.03	33.11
Min : Max	20.3 : 73.8	20.3 : 69.4	20.3 : 73.8
< 25	155 (1.7%)	155 (1.7%)	310 (1.7%)
[25-30[	2101 (22.6%)	2143 (22.9%)	4244 (22.7%)
[30-35[	3588 (38.5%)	3653 (39.0%)	7241 (38.8%)
[35-40[	2087 (22.4%)	2044 (21.8%)	4131 (22.1%)
≥ 40	1377 (14.8%)	1377 (14.7%)	2754 (14.7%)

Efficacy results:

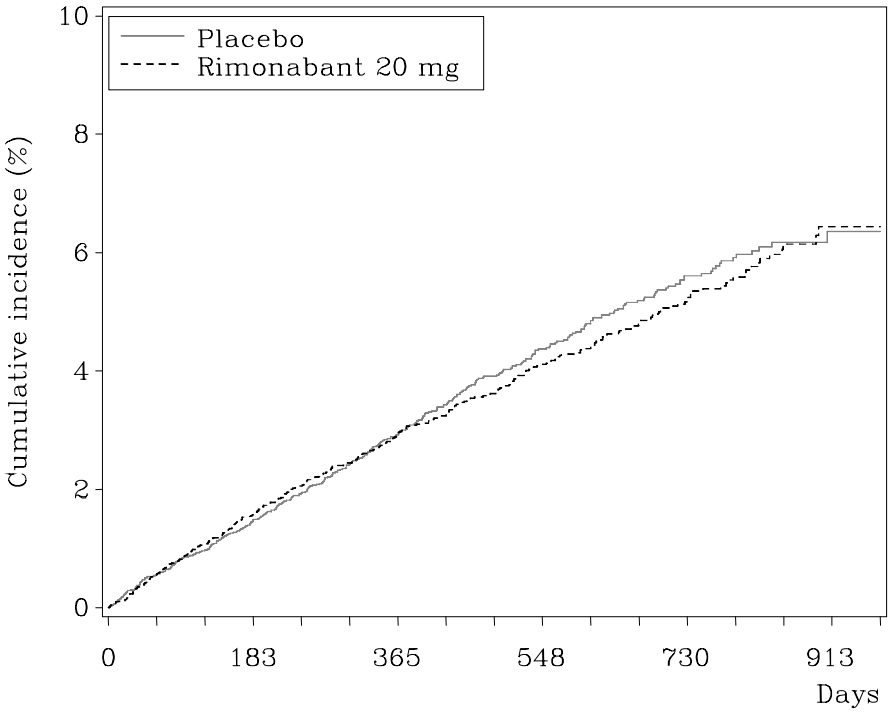
There was no significant difference in the time to first adjudicated MI, stroke, or cardiovascular death between those treated with rimonabant and those receiving placebo, with a hazard ratio of 0.97 (95% CI 0.84 to 1.121, p = 0.6799) (Table 5, Figure 1).

Table 5 - Adjudicated and confirmed cardiovascular events - Time to first MI, Stroke or CV death - ITT population

	Placebo (N=9314)	**Rimonabant 20 mg (N=9381)**
Number of events, n(%)	375 (4.0%)	364 (3.9%)
Total patient-year exposure	13212	13216
Number of events per 100 patient-year (95% CI)[a]	2.84 (2.55 to 3.13)	2.75 (2.47 to 3.04)
Cumulative incidence of events (95% CI)[b]		
Month 6	1.457 (1.209% to 1.705%)	1.568 (1.312% to 1.824%)
Month 12	2.922 (2.551% to 3.293%)	2.951 (2.580% to 3.321%)
Month 18	4.369 (3.886% to 4.852%)	4.109 (3.644% to 4.573%)
Month 24	5.606 (5.012% to 6.201%)	5.168 (4.602% to 5.733%)
Month 30	6.356 (5.585% to 7.127%)	6.438 (5.604% to 7.272%)
Log-rank test p-value[c] vs Placebo	-	0.6799
Hazard ratio (95% CI)[d] vs Placebo	-	0.97 (0.84 to 1.121)

[a] 95% CI calculated using a normal asymptotic distribution to the Poisson distribution
[b] Cumulative event rate calculated using Kaplan-Meier estimates and 95% CI derived using Greenwood's variance
[c] Pairwise Log-rank test of homogeneity between Planned arm
[d] Estimated using Cox proportional Hazard Model with Planned arm as the factor

Figure 1 - Adjudicated and confirmed cardiovascular events - Time to first MI, Stroke or CV death - ITT population - Kaplan-Meier cumulative incidence functions estimates



Number at risk:

Placebo	9314	7945	6110	4540	2654	476
Rimonabant 20 mg	9381	7921	6080	4532	2638	473

Events comprising the primary endpoint are summarized in Table 6.

Table 6 – Description of component events of the primary endpoint - ITT population

	Placebo (N=9314)	**Rimonabant 20 mg (N=9381)**
Number of patients with events		
n	375	364
Myocardial Infarction	139 (37.1%)	134 (36.8%)
Stroke	139 (37.1%)	131 (36.0%)
Cardiovascular death	92 (24.5%)	95 (26.1%)
Myocardial infarction + Stroke	1 (0.3%)	0
Myocardial infarction + Cardiovascular death	2 (0.5%)	2 (0.5%)
Stroke + Cardiovascular death	2 (0.5%)	2 (0.5%)

Only the first event in the composite endpoint MI, Stroke or CV death is counted

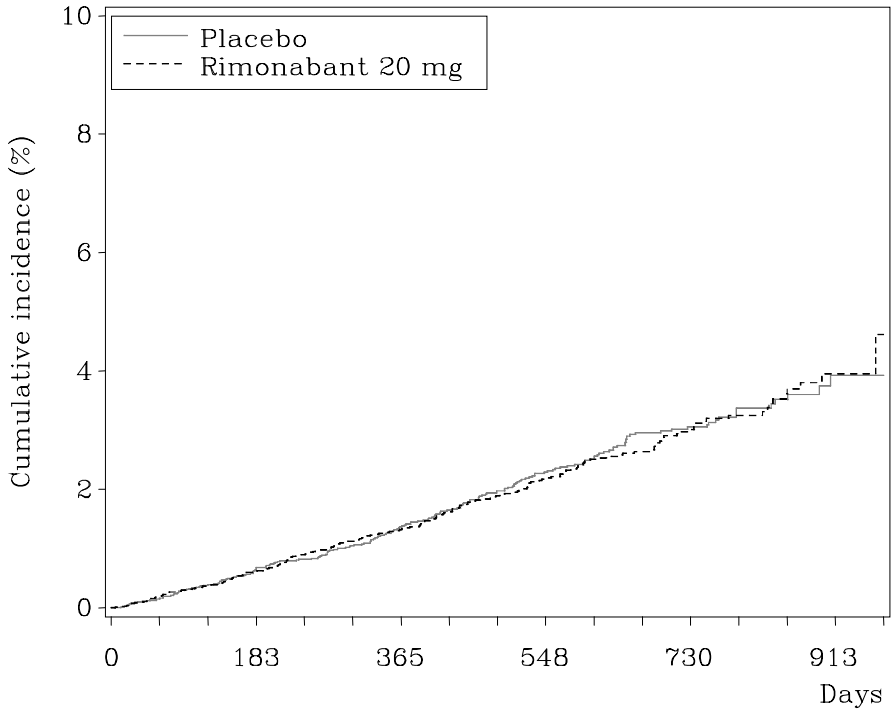
There was no difference in all-cause mortality between the 2 treatment groups, with a hazard ratio of 0.995 (95% CI 0.818 to 1.21, p = 0.9606). There was no evidence of any change in the incidence of deaths over the duration of the study (Table 7, Figure 2).

Table 7 - All cause mortality - Time to death - ITT population

	Placebo (N=9314)	Rimonabant 20 mg (N=9381)
Number of events, n(%)	201 (2.2%)	200 (2.1%)
Total patient-year exposure	13422	13428
Number of events per 100 patient-year (95% CI)[a]	1.50 (1.29 to 1.70)	1.49 (1.28 to 1.70)
Cumulative incidence of events (95% CI)[b]		
Month 6	0.640 (0.474% to 0.806%)	0.613 (0.451% to 0.774%)
Month 12	1.361 (1.104% to 1.618%)	1.316 (1.065% to 1.566%)
Month 18	2.289 (1.929% to 2.649%)	2.169 (1.821% to 2.517%)
Month 24	3.053 (2.602% to 3.503%)	2.974 (2.526% to 3.422%)
Month 30	3.930 (3.201% to 4.658%)	3.953 (3.249% to 4.657%)
Log-rank test p-value[c] vs Placebo	-	0.9606
Hazard ratio (95% CI)[d] vs Placebo	-	0.995 (0.818 to 1.21)

[a] 95% CI calculated using a normal asymptotic distribution to the Poisson distribution
[b] Cumulative event rate calculated using Kaplan-Meier estimates and 95% CI derived using Greenwood's variance
[c] Pairwise Log-rank test of homogeneity between Planned arm
[d] Estimated using Cox proportional Hazard Model with Planned arm as the factor

Figure 2 - All cause mortality - Time to death - ITT population - Kaplan-Meier cumulative incidence functions estimates



Number at risk:

Placebo	9314	8017	6228	4659	2739	488
Rimonabant 20 mg	9381	8006	6207	4652	2718	483

Safety results:

Overview of adverse events

The incidence of TEAEs and TEAEs leading to permanent treatment discontinuation was higher in the 20 mg rimonabant group (78.9% and 18.7%, respectively) compared with the placebo group (72.8% and 9.0%, respectively). The incidence of serious TEAEs and TEAEs leading to death were similar in the 2 treatment groups. An overview of patients with at least 1 TEAE is presented in Table 8.

Table 8 – Overview of TEAEs - randomized and exposed population

	Placebo (N=9302)	Rimonabant 20 mg (N=9369)
Patients with any TEAE	6770 (72.8%)	7389 (78.9%)
Patients with any serious TEAE	1642 (17.7%)	1607 (17.2%)
Patients with any TEAE leading to death	75 (0.8%)	68 (0.7%)
Patients with TEAE leading to permanent treatment discontinuation	837 (9.0%)	1748 (18.7%)

Note: TEAE: Treatment Emergent Adverse Event
TEAE includes all AEs with an onset date during treatment period and up to 75 days following the last study drug intake

Note: A TEAE leading to death was defined according to the date of onset of the adverse event and the outcome (death) regardless of the date of death, and therefore may have exceeded the efficacy on treatment period cut-off of 75 days after the end of treatment.

Summary of treatment-emergent adverse events

The primary system organ classes (SOC) in which TEAEs were reported more frequently with rimonabant, with a difference of $\geq$1%, were gastrointestinal disorders (32.9% versus 22.4% with placebo, driven by nausea and diarrhea), psychiatric disorders (32.3% versus 21.4%, respectively, driven by anxiety, depression, depressed mood, and insomnia), central nervous system disorders (31.1% versus 25.3%, respectively, driven by dizziness), general disorders and administration site disorders (19.0% versus 17.1%, respectively, driven by asthenia), metabolism and nutrition disorders (12.5% versus 10.1%, respectively), and skin and subcutaneous tissue disorders (10.6% versus 8.8%, respectively) (Table 9). All TEAEs are presented by SOC, high level group term, high level term, and preferred term in the CSR Appendix.

Table 9 - Number (%) of patients experiencing at least 1 TEAE (cut-off: incidence ≥5% in any treatment group) – randomized and exposed population

PRIMARY SYSTEM ORGAN CLASS Preferred Term	Placebo (N=9302) Number of events (%)	Patient-years	Rate[a]	Rimonabant 20 mg (N=9369) Number of events (%)	Patient-years	Rate[a]
GASTROINTESTINAL DISORDERS	2084 (22.4%)	11437	18.22	3083 (32.9%)	9483	32.51
Nausea	436 (4.7%)	13259	3.29	1362 (14.5%)	11337	12.01
Diarrhoea	521 (5.6%)	13155	3.96	760 (8.1%)	12068	6.30
PSYCHIATRIC DISORDERS	1989 (21.4%)	11615	17.12	3028 (32.3%)	9943	30.45
Anxiety	533 (5.7%)	13250	4.02	902 (9.6%)	12012	7.51
Depression	424 (4.6%)	13340	3.18	716 (7.6%)	12188	5.87
Depressed mood	317 (3.4%)	13402	2.37	539 (5.8%)	12400	4.35
Insomnia	427 (4.6%)	13277	3.22	521 (5.6%)	12385	4.21
NERVOUS SYSTEM DISORDERS	2349 (25.3%)	11046	21.27	2917 (31.1%)	9878	29.53
Dizziness	851 (9.1%)	12827	6.63	1202 (12.8%)	11673	10.30
INFECTIONS AND INFESTATIONS	2516 (27.0%)	10891	23.10	2299 (24.5%)	10414	22.08
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2151 (23.1%)	11376	18.91	1912 (20.4%)	10784	17.73
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1592 (17.1%)	12054	13.21	1781 (19.0%)	11119	16.02
Asthenia	319 (3.4%)	13478	2.37	479 (5.1%)	12468	3.84
METABOLISM AND NUTRITION DISORDERS	941 (10.1%)	12816	7.34	1171 (12.5%)	11661	10.04
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1169 (12.6%)	12619	9.26	1091 (11.6%)	11742	9.29
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1068 (11.5%)	12679	8.42	1032 (11.0%)	11845	8.71
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	818 (8.8%)	12847	6.37	994 (10.6%)	11818	8.41
VASCULAR DISORDERS	782 (8.4%)	12961	6.03	786 (8.4%)	12145	6.47
EYE DISORDERS	761 (8.2%)	12942	5.88	710 (7.6%)	12110	5.86
CARDIAC DISORDERS	702 (7.5%)	13053	5.38	612 (6.5%)	12337	4.96

PRIMARY SYSTEM ORGAN CLASS Preferred Term	Placebo (N=9302) Number of events (%)	Patient-years	Rate[a]	Rimonabant 20 mg (N=9369) Number of events (%)	Patient-years	Rate[a]
INVESTIGATIONS	574 (6.2%)	13214	4.34	553 (5.9%)	12382	4.47
RENAL AND URINARY DISORDERS	476 (5.1%)	13325	3.57	522 (5.6%)	12363	4.22
EAR AND LABYRINTH DISORDERS	382 (4.1%)	13380	2.86	419 (4.5%)	12477	3.36
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	416 (4.5%)	13416	3.10	372 (4.0%)	12537	2.97
BLOOD AND LYMPHATIC SYSTEM DISORDERS	279 (3.0%)	13522	2.06	295 (3.1%)	12607	2.34
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	248 (2.7%)	13488	1.84	249 (2.7%)	12617	1.97
HEPATOBILIARY DISORDERS	160 (1.7%)	13630	1.17	139 (1.5%)	12757	1.09
ENDOCRINE DISORDERS	81 (0.9%)	13692	0.59	70 (0.7%)	12811	0.55
IMMUNE SYSTEM DISORDERS	77 (0.8%)	13670	0.56	63 (0.7%)	12802	0.49
SURGICAL AND MEDICAL PROCEDURES	54 (0.6%)	13707	0.39	49 (0.5%)	12829	0.38
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	14 (0.2%)	13755	0.10	20 (0.2%)	12856	0.16
SOCIAL CIRCUMSTANCES	14 (0.2%)	13757	0.10	18 (0.2%)	12856	0.14

[a] Number of events per 100 patient-year
TEAE: treatment emergent adverse events, SOC: system organ class, PT: preferred term
MedDRA version 11.1
A patient may have AEs in more than one SOC and more than one PT
Table sorted by decreasing order of SOC frequency and decreasing order of PT frequency in a given SOC, based on incidence first in the rimonabant treatment group, and next in the placebo group
Only preferred term with a frequency ≥ 5% in at least on group are presented. All SOC with non-zero data are presented

Summary of serious adverse events

The incidence of serious TEAEs was similar in both groups (17.2% of patients in the rimonabant group versus 17.7% in the placebo group).

Serious psychiatric adverse events were reported by 2.5% of patients receiving rimonabant, compared to 1.3% of those receiving placebo. The difference was driven mainly by depression (0.4% with rimonabant versus 0.2% with placebo), aggression (0.2% versus <0.1%, respectively), suicidal ideation (0.9% versus 0.5%, respectively), which was to be reported as a serious adverse event by convention (implemented in February 2008), and visual hallucination (0.1% versus <0.1%, respectively). There was a minimal difference in major depression (0.4% versus 0.3%, respectively). The numerical differences in suicidal behavior (3 versus 2, respectively), suicide attempt (9 versus 5, respectively), and completed suicide (4 versus 1, respectively) did not result in a difference in percentage (<0.1% for each group).

Nervous system disorder serious adverse events were not different, reported by 1.8% of patients receiving rimonabant compared with 1.5% of those receiving placebo, but there were more reports of dizziness with rimonabant (0.2% versus <0.1%, respectively). There were no other differences in specific neurological events. Of note, seizure-related events (convulsion, epilepsy, grand mal convulsion, complex partial seizures, status epilepticus, and partial seizures) were reported in 26 patients receiving rimonabant (2 patients in rimonabant group had 2 different reported events: one patient had convulsion and status epilepticus, and one had epilepsy and grand mal convulsion) compared to 30 patients receiving placebo.

There were no differences $\geq$1% between rimonabant and placebo in the serious adverse events of infections and infestations (3.3% with rimonabant versus 3.9% with placebo), gastrointestinal disorders (2.1% in each group), musculoskeletal and connective tissue disorders (1.3% versus 1.9%, respectively), general disorders and administration site conditions (1.3% versus 1.2%, respectively), respiratory, thoracic, and mediastinal disorders (1.2% versus 1.6%, respectively), eye disorders (0.2% versus 0.4%, respectively), renal and urinary disorders (1.1% in each group), neoplasms (benign, malignant, and unspecified) (1.9% versus 2.4%, respectively), blood and lymphatic disorders (0.4% in each group), and hepatobiliary disorders (0.6% in each group). While there was also no difference in metabolism and nutrition disorders (1.1% in each group), there were more reports of hypoglycemia with rimonabant (0.3% versus 0.1% with placebo) and fewer reports of diabetes mellitus inadequate control (<0.1% versus 0.2%, respectively).

Please refer to the CSR Appendix for the summary table of all serious TEAEs and for details presented in the narratives.

Summary of deaths

The incidence of deaths was the same (2.6%) in both treatment groups (Table 10). Two hundred seventy-nine deaths (142 in the rimonabant group and 137 in the placebo group) were cardiovascular related. The non cardiovascular deaths were mainly due to various types of cancer and infections. Please refer to the CSR Appendix for a listing of the patients who died and for details presented in narratives for the non cardiovascular deaths.

Table 10 – Number (%) of patients who died, by analysis period

	Not Randomized (N=2)	Placebo (N=9314)	Rimonabant 20 mg (N=9381)
Any study period death	0	242 (2.6%)	243 (2.6%)
Any cardiovascular death	0	137 (1.5%)	142 (1.5%)
Non cardiovascular death	0	105 (1.1%)	101 (1.1%)
Pre treatment period death	0	1 (<0.1%)	0
Any cardiovascular death	0	1 (<0.1%)	0
Non cardiovascular death	0	0	0
On treatment period death	NA	163 (1.8%)	142 (1.5%)
Any cardiovascular death	NA	108 (1.2%)	95 (1.0%)
Non cardiovascular death	NA	55 (0.6%)	47 (0.5%)
Post treatment period death	NA	78 (0.8%)	101 (1.1%)
Any cardiovascular death	NA	28 (0.3%)	47 (0.5%)
Non cardiovascular death	NA	50 (0.5%)	54 (0.6%)

Notes: Entire study period = from the informed consent signed to the end of study
n(%) = number and percentage of patients who died
Category for death (cardiovascular or not) according to investigator

Summary of treatment-emergent adverse events leading to treatment discontinuation

Discontinuation due to TEAEs occurred more frequently in the rimonabant group (18.7% of patients) compared with patients in the placebo group (9.0%). The difference between groups was mainly due to the psychiatric disorders SOC (9.0% of patients in the rimonabant group versus 3.7% in the placebo group), gastrointestinal disorders SOC (5.2% versus 1.6%, respectively), and nervous system disorders SOC (3.3% versus 1.6%, respectively). Please refer to the CSR Appendix for the summary table of all TEAEs leading to permanent treatment discontinuation.

Conclusions: [redacted]

Date of report: 25-Jun-2009