SYNOPSIS

Title of the study: Randomized, multicenter, double-blind, placebo-controlled, two-arm parallel group trial of rimonabant 20-mg once daily (OD), for inhibition of atherosclerosis progression assessed by carotid artery intima-media thickness (CIMT), in overweight patients with additional risk factors (EFC5828)
Investigator: [redacted]
Study centers: The study was conducted at 65 centers in 6 countries (Canada, France, Spain, Netherlands, United Kingdom, and United States of America).
Publications (reference): None
Study period: Date first patient enrolled: 25 August 2005 Date last patient completed: 27 April 2009
Phase of development: Phase 3
Objectives: The objectives of the protocol were as follows: ***Primary***: To evaluate the effect of rimonabant 20 mg OD in comparison with placebo, on the quantitative progression of atherosclerosis as assessed by CIMT. ***Secondary***: To evaluate the safety and tolerability of the above rimonabant regimen in the study population of atherosclerotic patients. The study was stopped prematurely after all patients had been randomized (661 patients), due to the Sponsor's decision to discontinue the rimonabant development program. A total of 9 patients stopped treatment on or after 6 November 2008; three completed the treatment period and 6 were discontinued due to the Sponsor's decision under other reason. Thus, of the 661 patients randomized, 655 patients had completed or discontinued the treatment period and had corresponding efficacy and safety follow-up per protocol. Beyond the end of treatment visit, the monitoring for safety continued to be performed according to the protocol. The analysis (as defined in the statistical analysis plan) of these efficacy and safety data is presented through a synopsis-style report. Appendices attached to this synopsis-style report were chosen to provide the relevant information.
Methodology: This was a prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, 2-arm parallel group (rimonabant 20-mg OD vs placebo), stratified trial.

Number of patients: Planned: 600 Randomized: 661 Treated: 660

Evaluated: Efficacy (intent-to-treat [ITT]): 640 Safety (randomized and exposed patients) : 660

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 metabolic syndrome as defined by the presence of at least 2 of the following additional risk factors:

- Triglyceride level ≥150 mg/dL (1.69 mmol/L)
- High-density lipoprotein cholesterol <40 mg/dL (1.03 mmol/L) for men or 50 mg/dL (1.28 mmol/L) for women
- Fasting glucose ≥110 mg/dL (6.1 mmol/L)
- High blood pressure (≥140 mmHg systolic and/or ≥90 mmHg diastolic) at screening visit, or current treatment by antihypertensive medication

In addition, at Screening, it was required that the quantitative B-mode ultrasound imaging of the carotid arteries showed a CIMT measurement no less than 0.7 mm (ie, ≥0.7 mm) in either of the far walls of the common carotid artery and no greater than 3 mm (ie, <3 mm) in any carotid artery segment. All 6 carotid artery far wall segments were to allow for CIMT measurements as per protocol. The Screening CIMT recording was to be deemed of acceptable CIMT image quality, and demonstrate adherence to the CIMT interrogation protocol, as determined by assessment from the Imaging Core Laboratory.

Investigational product: SR141716 (rimonabant)

Dose: 20 mg tablet of rimonabant, once a day

Administration: Oral

Batch number(s): [redacted]

Duration of treatment: 30 to 32 months

Duration of observation: 35 to 36 months

Reference therapy: Placebo

Dose: Matched rimonabant tablet

Administration: Oral

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy:

Primary endpoint: The primary efficacy endpoint was the absolute change in averaged per patient CIMT in mm from Baseline to Month 30. For each ultrasound examination, CIMT measurements were combined to a per patient aggregate of 6 carotid segments, and each examination was measured by 2 independent image analysts.

Secondary endpoints: The secondary efficacy endpoint was the time (in days) from randomization to the first occurrence of any event of the following cluster: stroke, myocardial infarction, or cardiovascular death. The other secondary efficacy endpoint was the time from randomization to the first occurrence of any event of the following cluster: stroke, myocardial infarction, cardiovascular death, or hospitalization for revascularization procedure, unstable angina, or transient ischemic attack.

Safety: Only adverse events were reviewed and described.

Statistical methods:

Efficacy:

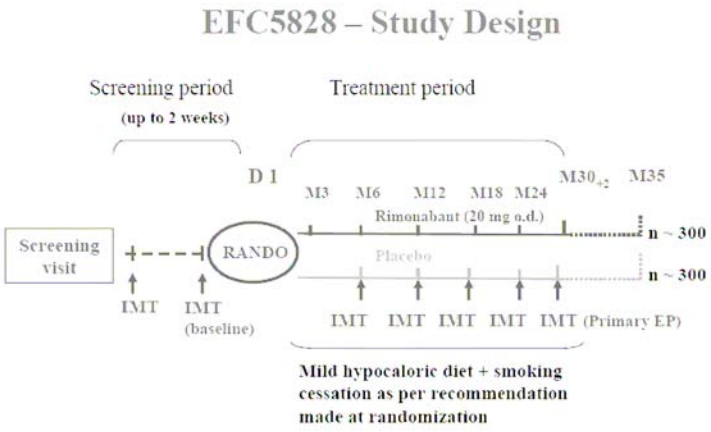
Primary endpoint: The primary analysis, performed on the ITT population, was a repeated measures linear mixed effects model. The model was specified in terms of fixed effects for treatment, time, carotid segment-by-image-analyst interaction, and treatment-by-time interaction. The dependent variable was the CIMT measurement at each segment for each image analyst from Screening to Month 30. Time in the model was a continuous variable expressed in years (time elapsed from randomization to CIMT examination). In addition, in case of non-normality of the distribution of the slopes of progression of the mean CIMT by patient, a nonparametric approach was to be used. The slopes of the progression of the CIMT by subject were compared between the 2 treatment groups using the exact nonparametric Wilcoxon test and the difference assessed using the Hodges-Lehmann estimator.

Secondary endpoints: Time to event parameters were analyzed in the all randomized population. The time from randomization to each defined clustered endpoint was compared between the 2 treatment groups using a 2-sided log-rank asymptotic test. Cumulative incidence functions in each treatment group were calculated and plotted using a nonparametric Kaplan-Meier estimate. Hazard ratio with 95% confidence interval was estimated using the Cox model with treatment group as the only factor.

Safety: Adverse events were coded according to 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 flow-chart is provided at the end of the document.



Summary of populations:

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

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

	Placebo (N=335)	Rimonabant 20 mg (N=326)
Randomized and exposed patients	335 (100%)	325 (99.7%)
Randomized but not exposed patients	0	1 (0.3%)
ITT population	327 (97.6%)	313 (96.0%)
Reason for exclusion from ITT population		
No post-randomization CIMT measurement	8 (2.4%)	13 (4.0%)
Completers population	228 (68.1%)	203 (62.3%)
Reason for exclusion from completers population		
No final CIMT at month 30 on treatment[a]	99 (29.6%)	110 (33.7%)

[a] Month 30 CIMT (≥ D810) considered on treatment if the date of CIMT ≤ last trt administration + 75 days

Patient disposition: A total of 660 patients were exposed to study drug. One patient from the rimonabant group was randomized, but not exposed to investigational product. A total of 451 patients completed the study treatment period as planned. The most common reason for discontinuing the study drug was an adverse event. Six patients (3 in each treatment group) discontinued the study drug after the sponsor's decision to stop of the study and were counted in the category "other reason". For these 6 patients, the end-of-treatment visit at Month 30 was performed as planned. Table 2 summarizes patient disposition including reasons for treatment discontinuation.

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

	Placebo (N=335)	Rimonabant 20 mg (N=326)
Patients randomized	335	326
Randomized but not exposed	0	1 (0.3%)
Randomized and exposed	335 (100%)	325 (99.7%)
Completed study treatment period	240 (71.6%)	211 (64.7%)
Did not complete the study treatment period	95 (28.4%)	114 (35.0%)
Reason for permanent study drug discontinuation		
Adverse event	40 (11.9%)	74 (22.7%)
Subject's request	34 (10.1%)	26 (8.0%)
Other reason	21 (6.3%)	14 (4.3%)

Exposure: The safety population in this study included 660 patients randomized and exposed to at least 1 dose of the investigational product. The mean number of months the patients were exposed to the investigational products was higher in the placebo group (25.44 months) than in the 20 mg rimonabant group (23.59 months). Patient exposure, based on the safety population, is presented in Table 3.

Table 3 - Summary of exposure to study drug - safety population

	Placebo (N=335)	Rimonabant 20 mg (N=325)
Cumulative exposure (patient years)	710.2	639
Extent of exposure (months)		
n	335	325
Mean (SD)	25.44 (8.72)	23.59 (10.34)
Median	29.70	29.67
Min : Max	0.3 : 33.7	0.1 : 32.9
< 6 months	28 (8.4%)	43 (13.2%)
[6-12[months	16 (4.8%)	22 (6.8%)
[12-18[months	16 (4.8%)	13 (4.0%)
[18-24[months	20 (6.0%)	23 (7.1%)
[24-30[months	153 (45.7%)	139 (42.8%)
[30-32[months	98 (29.3%)	82 (25.2%)
>= 32 months	4 (1.2%)	3 (0.9%)

Demographics: Patient demographic characteristics are presented in Table 4.

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

	Placebo (N=335)	Rimonabant 20 mg (N=326)	All (N=661)
Age (years)			
n	335	326	661
Mean (SD)	62.8 (5.7)	62.8 (6.0)	62.8 (5.8)
Median	62.0	61.0	62.0
Min : Max	55 : 81	55 : 84	55 : 84
Age group [n(%)]			
< 65	222 (66.3%)	210 (64.4%)	432 (65.4%)
[65-75[	101 (30.1%)	100 (30.7%)	201 (30.4%)
≥ 75	12 (3.6%)	16 (4.9%)	28 (4.2%)
Gender [n(%)]			
n	335	326	661
Male	165 (49.3%)	170 (52.1%)	335 (50.7%)
Female	170 (50.7%)	156 (47.9%)	326 (49.3%)
Race [n(%)]			
N	335	326	661

Caucasian	317 (94.6%)	314 (96.3%)	631 (95.5%)
Black	13 (3.9%)	8 (2.5%)	21 (3.2%)
Asian / Oriental	3 (0.9%)	4 (1.2%)	7 (1.1%)
Other	2 (0.6%)	0	2 (0.3%)
Ethnicity			
American hispanic	4 (1.2%)	2 (0.6%)	6 (0.9%)
Height (cm)			
n	335	326	661
Mean (SD)	169.4 (10.1)	169.5 (9.9)	169.5 (10.0)
Median	170.0	169.0	169.0
Min : Max	144 : 198	145 : 193	144 : 198
Waist circumference (cm)			
n	335	326	661
Mean (SD)	112.27 (12.16)	111.61 (11.79)	111.95 (11.98)
Median	110.33	110.50	110.33
Min : Max	89.3 : 163.3	89.0 : 158.0	89.0 : 163.3
Waist circumference [n(%)]			
≤ 88 cm (F); ≤ 102 cm (M)	2 (0.6%)	3 (0.9%)	5 (0.8%)
> 88 cm (F); > 102 cm (M)	333 (99.4%)	323 (99.1%)	656 (99.2%)
Weight (kg)			
n	335	324	659
Mean (SD)	97.50 (17.65)	97.00 (17.40)	97.25 (17.52)
Median	94.50	95.95	95.00
Min : Max	66.5 : 160.6	53.6 : 175.4	53.6 : 175.4
BMI (kg/m²)			
n	335	324	659
Mean (SD)	34.02 (5.93)	33.77 (5.38)	33.90 (5.66)
Median	32.73	32.80	32.77
Min : Max	24.0 : 69.5	21.2 : 57.9	21.2 : 69.5
BMI group [n(%)]			
< 25	1 (0.3%)	4 (1.2%)	5 (0.8%)
[25-30[	86 (25.7%)	74 (22.7%)	160 (24.2%)
[30-35[	129 (38.5%)	138 (42.3%)	267 (40.4%)
[35-40[	68 (20.3%)	69 (21.2%)	137 (20.7%)
≥ 40	51 (15.2%)	39 (12.0%)	90 (13.6%)

Efficacy results:

- **Primary efficacy endpoint**

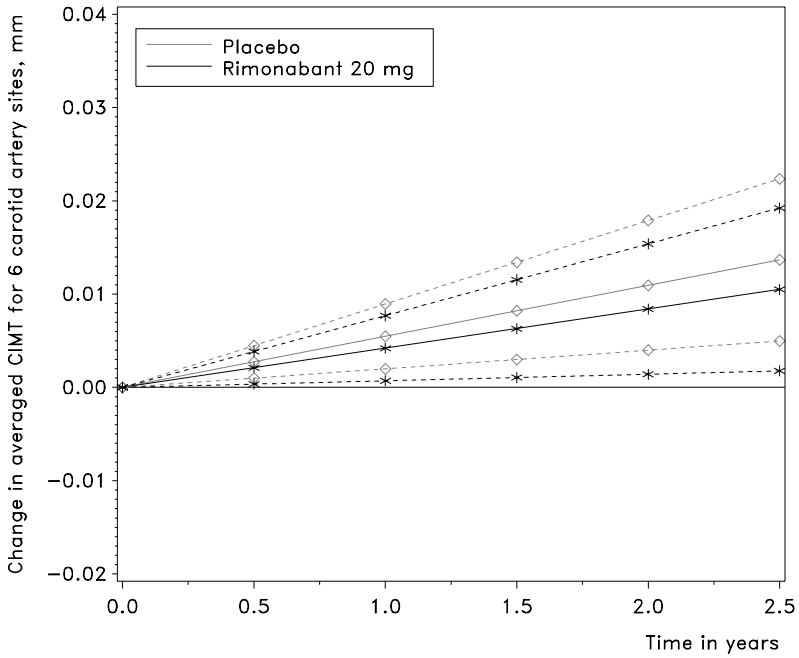
A low progression of CIMT was observed in both the placebo and rimonabant 20 mg treatment groups. There was no difference between the 2 treatment groups for this primary efficacy endpoint (Table 5, Figure 1, and Table 6).

Table 5 - Covariance analysis of the absolute change in averaged per patient CIMT for 6 segments - ITT population

Averaged CIMT for 6 carotid artery sites	Placebo (N=327)	Rimonabant 20 mg (N= 313)
Baseline		
Estimate (SE)	0.8301 (0.00908)	0.8137 (0.00928)
95% CI	[0.8123 to 0.8479]	[0.7955 to 0.8319]
Month 30		
Estimate (SE)	0.8438 (0.00969)	0.8242 (0.00988)
95% CI	[0.8247 to 0.8628]	[0.8048 to 0.8436]
Progression in CIMT per year (mm/yr)		
Estimate (SE)	0.00547 (0.001775)	0.00420 (0.001783)
95% CI	[0.00199 to 0.00895]	[0.00071 to 0.00769]
p-value[a,b]	0.0021	0.0185
Estimate difference in progression vs Placebo (SE)[a]		-0.00127 (0.002515)
95% CI vs Placebo[a]		[-0.00620 to 0.00366]
p vs Placebo[a]		0.6137

CI: Confidence Interval - CIMT: carotid intima-media thickness
[a]Using repeated measurements nalysis of covariance with time, planned arm, carotid segment by image analyst interaction, and planned arm by time interaction as fixed effect
[b]Within planned arm group versus no change

Figure 1 – Change in averaged CIMT for the primary endpoint – ITT population



Lines were estimated from the statistical model based on the 6 carotid artery sites measured by two independent image analysts.
Dotted lined indicated 95% confidence intervals.

Table 6 – Comparison of the slopes of progression of averaged per patient CIMT for the 6 segments using a nonparametric approach

Averaged CIMT for 6 carotid artery sites	Placebo (N=327)	Rimonabant 20 mg (N=313)
Progression in CIMT per year (mm/yr)		
n	327	313
Median	0.00305	0.00259
Q1 - Q3	-0.01270 : 0.02138	-0.01168 : 0.01687
Min : Max	-0.1364 : 0.2645	-0.1236 : 0.2141
Hodges Lehmann estimate of the difference vs Placebo	-	-0.00076
Hodges Lehmann 95% CI	-	[-0.00495 to 0.00334]
p vs Placebo [a]	-	0.7223

The slopes by subject are assessed through regression linear models.
[a] using Wilcoxon rank sum test

- **Secondary efficacy endpoints**

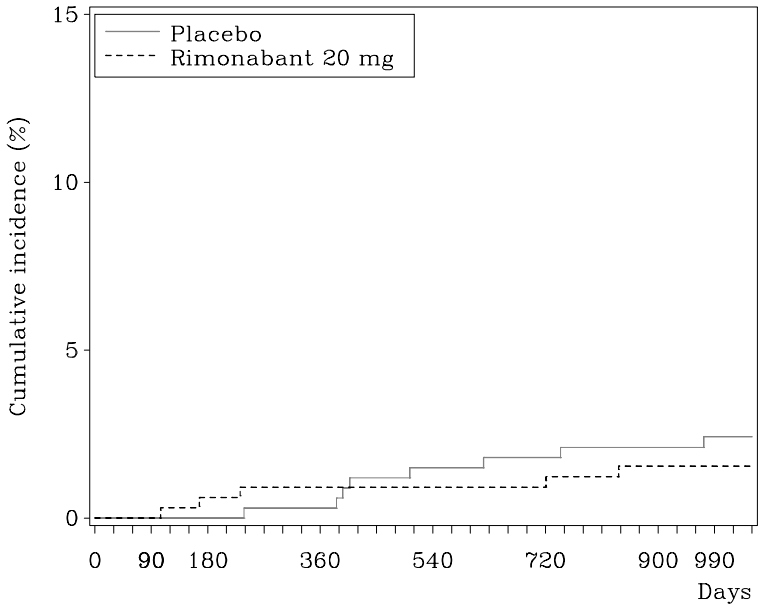
There were 5 patients who died due to cardiovascular related events (2 in the rimonabant group and 3 in the placebo group). As displayed in Table 7 and Figure 2, there was no significant difference between the 2 treatment groups in the time to first occurrence of stroke, myocardial infarction, or cardiovascular death. Analyses of the secondary endpoints are provided in Appendix (not disclosed).

Table 7 - Time to first stroke, myocardial infarction, or cardiovascular death – All randomized population

	Placebo (N=335)	Rimonabant 20 mg (N=326)
Number of events, n	8	5
Median survival (day) (95% CI)[a]	NC (NC to NC)	NC (NC to NC)
Cumulative incidence of events (95% CI)[a]		
Day 90	0.000 (0.000% to 0.000%)	0.000 (0.000% to 0.000%)
Day 180	0.000 (0.000% to 0.000%)	0.613 (0.000% to 1.461%)
Day 360	0.299 (0.000% to 0.885%)	0.922 (0.000% to 1.961%)
Day 540	1.500 (0.195% to 2.804%)	0.922 (0.000% to 1.961%)
Day 720	1.802 (0.373% to 3.231%)	0.922 (0.000% to 1.961%)
Day 900	2.107 (0.563% to 3.651%)	1.551 (0.202% to 2.901%)
Day 1050	2.426 (0.765% to 4.087%)	1.551 (0.202% to 2.901%)
Log-rank test p-value[b]		
vs Placebo	-	0.4298
Hazard ratio (95% CI)[c]		
vs Placebo	-	0.64 (0.209 to 1.956)

[a]Kaplan-Meier estimates [b]Pairwise Log-rank test of homogeneity between Planned arm [c]Estimated using Cox proportional Hazard Model with Planned arm as the factor

Figure 2 - Time to first stroke, myocardial infarction, or cardiovascular death – All randomized population



Number at risk:								
Placebo	335	335	335	333	326	324	311	305
Rimonabant 20 mg	326	326	324	321	321	320	308	303

Safety results:

- **Overview of adverse events**

The incidence of treatment-emergent adverse events (TEAEs) was higher in the 20 mg rimonabant group (95.7% of patients) compared with the placebo group (91.6%), as well as the incidence of TEAEs leading to discontinuation of investigational product (22.8% versus 11.9%). The incidence of serious TEAEs was similar in both treatment groups (17.5% versus 16.7%). There were 5 noncardiovascular deaths. An overview of patients with at least 1 TEAE is presented in Table 8.

Table 8 - Overview of TEAEs - safety population

	Placebo (N=335)	Rimonabant 20 mg (N=325)
Any TEAE	307 (91.6%)	311 (95.7%)
Any serious TEAE	56 (16.7%)	57 (17.5%)
Any TEAE leading to Death	2 (0.6%)	3 (0.9%)
Any TEAE leading to permanent treatment discontinuation	40 (11.9%)	74 (22.8%)

Notes : Treatment emergent adverse event (TEAE):
Any adverse event that developed or worsened during the on-treatment period(from the first study drug intake to 75 days after the last study drug intake, or end date, whichever comes first)
n(%) = number and percentage of patients with at least one adverse event

- **Summary of treatment-emergent adverse events**

The most commonly reported TEAEs in the 20 mg rimonabant group belonged to the nervous system disorders system organ class (SOC) (47.1% versus 38.5% in the placebo group). Treatment-emergent adverse events in the rimonabant group were also frequently reported in the psychiatric disorders SOC (42.5% versus 31.0% in the placebo group) and gastrointestinal disorders SOC (40.6% versus 31.6% in the placebo group) (Table 9). All TEAEs are presented by SOC, high level group term, high level term, and PT in Appendix (not disclosed).

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

Primary System Organ Class Preferred Term	Placebo (N=335)	Rimonabant 20 mg (N=325)
Any TEAE	307 (91.6%)	311 (95.7%)
Nervous system disorders	129 (38.5%)	153 (47.1%)
Dizziness	46 (13.7%)	71 (21.8%)
Paraesthesia	32 (9.6%)	32 (9.8%)
Headache	26 (7.8%)	23 (7.1%)
Hypoaesthesia	13 (3.9%)	22 (6.8%)
Psychiatric disorders	104 (31.0%)	138 (42.5%)
Depression	35 (10.4%)	47 (14.5%)
Anxiety	28 (8.4%)	39 (12.0%)
Insomnia	27 (8.1%)	33 (10.2%)
Depressed mood	18 (5.4%)	27 (8.3%)
Musculoskeletal and connective tissue disorders	143 (42.7%)	136 (41.8%)

Arthralgia	34 (10.1%)	27 (8.3%)
Back pain	32 (9.6%)	25 (7.7%)
Pain in extremity	23 (6.9%)	24 (7.4%)
Myalgia	17 (5.1%)	16 (4.9%)
Infections and infestations	178 (53.1%)	132 (40.6%)
Nasopharyngitis	58 (17.3%)	34 (10.5%)
Influenza	30 (9.0%)	27 (8.3%)
Upper respiratory tract infection	28 (8.4%)	19 (5.8%)
Bronchitis	25 (7.5%)	18 (5.5%)
Urinary tract infection	18 (5.4%)	11 (3.4%)
Gastrointestinal disorders	106 (31.6%)	132 (40.6%)
Nausea	17 (5.1%)	63 (19.4%)
Diarrhoea	12 (3.6%)	30 (9.2%)
Vomiting	7 (2.1%)	22 (6.8%)
General disorders and administration site conditions	91 (27.2%)	90 (27.7%)
Asthenia	15 (4.5%)	23 (7.1%)
Fatigue	26 (7.8%)	18 (5.5%)
Oedema peripheral	30 (9.0%)	11 (3.4%)
Injury, poisoning and procedural complications	78 (23.3%)	60 (18.5%)
Fall	29 (8.7%)	24 (7.4%)
Skin and subcutaneous tissue disorders	62 (18.5%)	59 (18.2%)
Hyperhidrosis	9 (2.7%)	21 (6.5%)
Eye disorders	61 (18.2%)	49 (15.1%)
Cataract	17 (5.1%)	13 (4.0%)

Notes: n(%) = number and percentage of patients with at least one adverse event, 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.
In case of equal frequency regarding SOC (resp. PT), alphabetical order is used.
Only SOC with at least one PT with an incidence >= 5% in at least one group are presented.

- **Summary of serious adverse events**

The incidence of serious TEAEs was similar in both groups (17.5% of patients in the rimonabant group versus 16.7% in the placebo group). Serious TEAEs that were frequently reported in the rimonabant group belonged to the SOCs of benign, malignant, and unspecified neoplasms (3.7% versus 2.4% in the placebo group), psychiatric disorders (2.5% versus 1.5%, respectively), injury, poisoning, and procedural complications (2.5% versus 1.5%, respectively), and gastrointestinal disorders SOC (2.5% versus 2.7%, respectively).

Three patients (0.9%) in the rimonabant group and 3 patients (0.9%) in the placebo group reported suicidal ideation. This event was considered, by convention (implemented in February 2008), to be a serious adverse event for 2 patients (0.6%) and 3 patients (0.9%), respectively. One patient in the rimonabant group had suicidal ideation reported as a TEAE only. Only patients in the placebo group discontinued investigational product due to suicidal ideation. Appendix (not disclosed) contains details presented in the narratives for the 5 patients that were reported to have serious TEAEs.

- **Summary of deaths**

There was an equal number of deaths (5 each) in both treatment groups (Table 10). Five deaths (2 in the rimonabant group and 3 in the placebo group) were cardiovascular related. The non cardiovascular deaths were due to various types of cancer. Please refer to Appendix (not disclosed) for a listing of the patients who died and Appendix (not disclosed) for details presented in narratives for the non-cardiovascular deaths.

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

	Not Randomized (N=1387)	Placebo (N=335)	Rimonabant 20 mg (N=326)
Any study period death	0	5 (1.5%)	5 (1.5%)
Any cardiovascular death	0	3 (0.9%)	2 (0.6%)
Non cardiovascular death	0	2 (0.6%)	3 (0.9%)
Pre treatment period death	0	0	0
Any cardiovascular death	0	0	0
Non cardiovascular death	0	0	0
On treatment period death	NA	2 (0.6%)	2 (0.6%)
Any cardiovascular death	NA	2 (0.6%)	1 (0.3%)
Non cardiovascular death	NA	0	1 (0.3%)
Post treatment period death	NA	3 (0.9%)	3 (0.9%)
Any cardiovascular death	NA	1 (0.3%)	1 (0.3%)
Non cardiovascular death	NA	2 (0.6%)	2 (0.6%)

Notes: Entire study period = from the informed consent signed to the end of study
n(%) = number and percentage of patients who died

- **Summary of treatment-emergent adverse events leading to treatment discontinuation**

Discontinuation due to TEAEs occurred more frequently in the rimonabant group (22.8% of patients) compared with the placebo group (11.9%). The difference between groups was mainly due to the nervous system disorders SOC (4.6% of patients in the rimonabant group versus 2.4% in the placebo group), the psychiatric disorders SOC (9.5% versus 4.5%, respectively), and the gastrointestinal disorders SOC (.4.6% versus 1.8%, respectively).

Conclusions: [redacted]
Date of report: 19-June-2009