SYNOPSIS

Title of the study:	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 (Study number: PM-C-0172).
Investigator:	No principal investigator.
Study centers:	The main study was conducted in 27 active study centers in 9 countries (Canada, Denmark, France, Finland, Italy, Spain, Sweden, United Kingdom [UK], and United States [US]). A total of 4 study sites were selected in the US for the sub-study.
Publications (reference): None	
Study period:	
Date first patient enrolled:	20 February 2006
Date last patient completed:	24 July 2008
Phase of development: Phase 3b	

Objectives:

The objectives of the protocol were as follows:

Primary: To assess the effect of rimonabant on visceral fat area over a period of 12 months when prescribed with a mild hypocaloric diet (-600 kcal/day from the calculated energy expenditure) in abdominally obese patients with metabolic syndrome.

Secondary:

- To assess the effect of rimonabant over a period of 12 months on:
  - Liver fat content using Computed Tomography (CT) scan
  - Anthropometric measures (weight, Waist Circumference [WC], body composition using Dual Energy X-ray Absorptiometry [DEXA])
  - Lipid, lipoprotein profile
  - Glycemia, insulinemia and Hemoglobin A_{1c} (HbA_{1c})
  - Adipokines, inflammatory and hemostatic markers
- To evaluate the percentage of patients with metabolic syndrome at 12 months
- To evaluate the safety and tolerability of rimonabant in these patients.

In four selected US sites (sub-study), the following additional measurements were performed:

- Basal lipolysis and insulin suppressed lipolysis (euglycemic hyperinsulinemic clamp). No Oral Glucose Tolerance Test (OGTT) was performed in these patients,
- Resting metabolic rate and substrate oxidation at rest using indirect calorimetry,
- Abdominal subcutaneous adipose tissue biopsy (for the evaluation of size/number of adipocytes and gene expression changes).

Due to the Sponsor's decision to discontinue the rimonabant clinical program, the analysis (as defined in the Statistical Analysis Plan [SAP]) focused on the primary efficacy endpoint, and on a review of the safety profile based on reporting of adverse events. The data which are presented in this synopsis report are also supported by limited appendices.

Methodology: This was a phase-III_b randomized, double-blind, placebo-controlled, two-parallel group, fixed dose (20 mg of rimonabant once daily), multicenter, international study.

Number of patients:

Main Study: Planned: 232 patients	Randomized: 254 patients	Treated: 254 patients
Sub-Study: Planned: 48 patients	Randomized: 68 patients	Treated: 68 patients

Evaluated:

Main Study: 210 patients

Sub-Study: 42 patients

Diagnosis and criteria for inclusion: Abdominally obese patients (WC > 102 cm in men and > 88 cm in women), male or female ≥ 35 years and ≤ 70 years old, with at least two other components of the metabolic syndrome were considered for enrollment in the study after giving his/her written informed consent.

Investigational product: White-opaque tablet containing 20 mg of active rimonabant with oral administration, once a day, in the morning (batch numbers: [redacted]).

Duration of treatment: 12 months (from Day (D) 1 post-randomization to D365 ± 14)

Duration of observation: Main study: 15 months / **Sub-study: 17** months

Reference therapy: White-opaque tablet containing 20 mg of placebo with oral administration, once a day, in the morning (batch numbers: [redacted].

Criteria for evaluation:

Efficacy: The following efficacy data were analyzed and reported for the main study:

Primary

- Relative change ($\frac{X_f - X_i}{X_i} \times 100$) from baseline to Month (M) 12 in visceral fat area assessed by CT scan (slice L4-L5).

Secondary:

- Absolute change from baseline in visceral fat area assessed by CT scan (slice L4-L5).
- Relative ($\frac{X_f - X_i}{X_i} \times 100$) and absolute changes from baseline to M12 in:
  - Other CT scan parameters assessing abdominal adiposity.
  - Liver fat content measured using CT scan (slice T12-L1) so as to measure liver/spleen relative density (liver/spleen ratio).
  - Anthropometric measures: weight, WC, body composition assessed by DEXA, Body Mass Index (BMI) derived from weight and height.
  - Specific lipid parameters: Plasma total cholesterol, plasma HDL Cholesterol (HDL-C), plasma LDL Cholesterol (LDL-C), plasma Triglycerides (TG), cholesterol content of HDL_2 and HDL_3 subfractions, HDL particle size, indices of LDL size, apolipoproteins B, A1 and CIII, Free Fatty Acid (FFA).
  - Glucose control parameters: Fasting glucose, fasting insulin, HbA_1c, OGTT (blood samples just before, 30 minutes, 60 minutes and 2 hours after an oral administration of 75 g of glucose for the measurement of glucose and insulin).
  - Adipokines, inflammatory and hemostatic markers: leptin, adiponectin, High Sensitivity C-Reactive Protein (hs-CRP), fibrinogen, Interleukin 6 (IL6), Tumor Necrosis Factor α (TNF α), Plasminogen Activator Inhibitor-1 (PAI-1).
- Percentages of patients with a metabolic syndrome at 12 months (National Cholesterol Education Program [NCEP] - Adult Treatment Panel III [ATPIII] criteria).

Sub-study : In 4 selected US sites for the sub-study, the additional evaluations were performed at baseline and 12-month visit:

- Basal lipolysis and insulin suppressed lipolysis (euglycemic hyperinsulinemic clamp). No OGTT was performed in these patients
- Resting metabolic rate and substrate oxidation at rest using indirect calorimetry
- Adipose tissue histology and expression of genes involved in glucose and lipid metabolism (superficial adipose tissue biopsy).

Results of the sub-study are provided in Appendix [redacted]

Safety: Only Adverse Events (AEs) were reviewed and described in this synopsis. Standard hematology and blood chemistry, physical examination, vital signs and Electrocardiogram (ECG) are provided in Appendix [redacted]

Statistical methods:

Efficacy: All efficacy analyses were performed on both Intent-To-Treat (ITT) and Per Protocol (PP) populations.

Primary efficacy analysis:

- Primary analysis of the primary efficacy variable

The relative change from baseline to M12 endpoint in visceral fat area (surface of Visceral Adipose Tissue [VAT]) was analyzed using Analysis of Covariance (ANCOVA) with treatment as fixed effect and baseline value as covariate. The Least-Squares Means (LSMEANS) change from baseline to week 12 endpoint and its Standard Error (SE) were presented for each treatment group along with the 95% Confidence Interval (CI). The difference in the LSMEANS between rimonabant 20 mg and placebo was calculated along with the 95% CI and the p-value for the difference.

- Other analyses of the primary efficacy variable

The primary analysis of the primary efficacy variable as above-defined was repeated either adding country or gender as fixed effect in the ANCOVA model, and for each gender.

Secondary efficacy analyses: Overall, secondary efficacy parameters were analyzed similarly to the primary efficacy variable. Descriptive statistics were presented. Additional analyses were also performed on the following variables:

- Body weight, BMI and WC: Values across time were graphically represented by gender and overall.

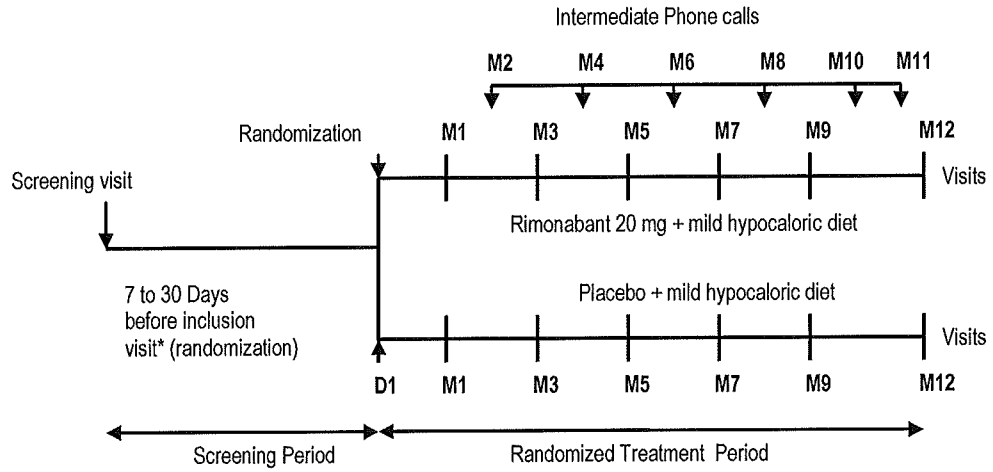
- CT scan parameters: Dot plot displaying patient values at baseline versus M12 endpoint were presented. In addition, gender was added as fixed effect in the ANCOVA model used for the primary analysis.

- Glucose profile from OGTT: At M12, the comparison between treatment groups on the glucose evolution parameter was done using a Chi^2 test.

- Metabolic Syndrome: At M12, treatment groups were compared using a Chi^2 test (or Fischer's exact test).

Safety: Safety analyses were carried out on the safety population. Treatment Emergent Adverse Events (TEAEs) were summarized (by treatment group and overall) using descriptive statistics. Other safety variables included pre- and post-treatment AEs, neurological and depression related Complementary Data Queries (CDQs), laboratory evaluation, physical examination, vital signs, ECG and pregnancy test.

Summary: A study flow-chart is provided at the end of the document, and a summary of the study design is provided as follows:



*may be extended up to 12 weeks for patients participating in the sub-study.

Summary of populations:

Populations	Placebo		Rimonabant 20 mg		Total	
Randomized population	129	(100.0%)	125	(100.0%)	254	(100.0%)
Males	60	(100.0%)	58	(100.0%)	118	(100.0%)
Females	69	(100.0%)	67	(100.0%)	136	(100.0%)
ITT population	112	(86.8%)	98	(78.4%)	210	(82.7%)
Males	47	(78.3%)	43	(74.1%)	90	(76.3%)
Females	65	(94.2%)	55	(82.1%)	120	(88.2%)
PP population	87	(67.4%)	65	(52.0%)	152	(59.8%)
Males	37	(61.7%)	29	(50.0%)	66	(55.9%)
Females	50	(72.5%)	36	(53.7%)	86	(63.2%)
Safety population	129	(100.0%)	125	(100.0%)	254	(100.0%)
Males	60	(100.0%)	58	(100.0%)	118	(100.0%)
Females	69	(100.0%)	67	(100.0%)	136	(100.0%)

Randomized population: all patients for whom the Interactive Voice Response System (IVRS) was called and for whom an IVRS number was allocated following the phone contact.
Safety population: all randomized patients who received at least one dose (tablet) of the study drug.
ITT population: all randomized patients who received at least one dose (tablet) of the study drug and who were evaluable for the primary efficacy variable, i.e. who had a visceral fat area value at both baseline and M12 endpoint, regardless the time of assessment since the last drug intake.
PP population: all ITT patients who did not meet any major protocol deviation at baseline or during the course of the study.

Patient disposition:

Overall, 59 randomized patients (23.2%), who received at least one dose of the study drug, were withdrawn from the study during the treatment period for reasons reported in the following table:

Withdrawals during the treatment period (Safety population)	Placebo N=129		Rimonabant 20 mg N=125		Total N=254	
All withdrawals	18	(14.0%)	41	(32.8%)	59	(23.2%)
Adverse event	8	(6.2%)	25*	(20.0%)	33*	(13.0%)
Poor compliance to protocol	0	(0.0%)	1	(0.8%)	1	(0.4%)
Subject's request	6	(4.7%)	7	(5.6%)	13	(5.1%)
Subject lost to follow-up	3	(2.3%)	6	(4.8%)	9	(3.5%)
Other reason	1	(0.8%)	2	(1.6%)	3	(1.2%)

* One patient [redacted] in the rimonabant group was withdrawn due to pre-treatment adverse event (not TEAE).

The most important reason was the occurrence of AE (13.0%) with a higher frequency reported in the rimonabant 20 mg group (20.0%) compared with the placebo group (6.2%). Other withdrawals were due to subject's request (5.1%), lost to follow-up (3.5%), other reason (1.2%) and poor compliance to the protocol (0.4%) and were comparable between both treatment groups.

Exposure:

Extent of exposure and treatment compliance were assessed from the safety population as follows:

Extent of exposure	Placebo N=129	Rimonabant 20 mg N=125	Total N=254
Exposure to study drug (Overall treatment period)			
N	110	84	194*
n (%) exposed from V2 (D1) to V8 (M12)	110 (100.0%)	84 (100.0%)	194 (100.0%)
Duration of exposure (days)**			
N	129	125	254
Mean (SD)	335.4 (82.87)	291.5 (119.56)	313.8 (104.71)
Median	364.0	361.0	363.0
Min/Max	3 / 399	1 / 389	1 / 399
Compliance to study drug*(%) (Overall treatment period)**			
N	126	120	246
Mean (SD)	97.16 (5.069)	96.90 (8.191)	97.03 (6.761)
Median	99.15	98.95	99.05
Min/Max	66.3 / 104.2	36.4 / 118.7	36.4 / 118.7

* One patient [redacted] with no extent of exposure as his exposure to the treatment period was not filled in from V6 (M7) to V7 (M9). His duration of exposure was derived according to first dose and last dose as stated in the SAP.

** Duration of exposure (days) = (Date of last dose of study drug - Date of first dose of study drug) + 1, ignoring temporary drug discontinuation(s). For missing date of last dose the study drug dispensing date was used, or, the patient's last visit date was used when the patient's last study drug dispensing date was missing. Student T-Test comparing treatment groups, $p < 0.001$.

*** % compliance = 100 x (Number of tablets taken / (Duration of exposure x 1 tablet per day)) rounded up to one decimal place.

The mean compliance was similar in both groups (97.16 ± 5.069% in the placebo group versus 96.90 ± 8.191% in the rimonabant group), while the mean duration of exposure was significantly longer in the placebo group (335.4 ± 82.87 days) than in the rimonabant group (291.5 ± 119.56 days) ($p < 0.001$).

Demographics:

Demographic characteristics and body measurements of the randomized population measured at baseline are summarized in the following table:

Demographics	Placebo N=129	Rimonabant 20 mg N=125	Total N=254
Age* (years)			
Mean (SD)	52.7 (8.04)	52.9 (9.19)	52.8 (8.61)
Median	53.0	52.0	53.0
Min/Max	35 / 69	35 / 70	35 / 70
Gender (n, %)			
Males	60 (46.5%)	58 (46.4%)	118 (46.5%)
Females	69 (53.5%)	67 (53.6%)	136 (53.5%)
Ethnic origin (n, %)			
Caucasian	124 (96.1%)	120 (96.0%)	244 (96.1%)
Black	5 (3.9%)	5 (4.0%)	10 (3.9%)
BMI (kg/m^2)**			
Mean (SD)	34.68 (3.820)	34.06 (3.207)	34.38 (3.538)
Median	34.90	33.70	34.20
Min/Max	25.8 / 41.0	26.9 / 40.5	25.8 / 41.0
WC (cm)			
Mean (SD)	112.02 (11.056)	111.97 (9.440)	112.00 (10.272)
Median	111.70	111.50	111.60
Min/Max	88.9 / 140.2	93.6 / 135.3	88.9 / 140.2

* Age in years calculated as integer (date of V1 - date of birth)/ 365.25.

All demographic and baseline characteristics were similar in both treatment groups. The majority of patients were female (53.5%) and Caucasian (96.1%). The mean patient age was 52.8 ± 8.61 years. Approximately half of the patients belonged to either [18-50] age group or [51-65] age group (44.5% and 48.8%, respectively). The mean BMI was 34.38 ± 3.538 kg/m² with a range of [25.8 – 41.0] kg/m². Most subjects were in the [30-35[BMI class and [35-40[BMI class (46.9% and 40.6%, respectively). The same proportion of patients had a metabolic syndrome, i.e. met at least 3 of the 5 defined criteria (87.2% in the rimonabant 20 mg group versus 87.6% in the placebo group), and each criterion was similarly found in both groups.

Efficacy Results:

Results of the primary efficacy endpoint in the ITT population are presented in the table below:

Visceral Fat Area (Surface of VAT)	Placebo N=112	Rimonabant 20 mg N=98	Difference (Rimonabant 20 mg - Placebo)
Baseline (cm²)			
Mean (SD)	214.45 (71.375)	221.03 (71.260)	
Median	202.35	209.80	
Min/Max	86.9 / 423.4	110.0 / 459.3	
M12 endpoint (cm²)			
Mean (SD)	201.07 (78.036)	172.44 (78.771)	
Median	186.00	155.10	
Min/Max	50.8 / 419.3	52.8 / 395.9	
Relative Change from Baseline to M12 Endpoint (%) by ANCOVA			
LSMEANS (SE)	-5.72 (2.025)	-22.52 (2.165)	-16.80 (2.966)
95% CI	-9.71 ; -1.73	-26.78 ; -18.25	-22.64 ; -10.95
p-value			<0.001

ANCOVA model: Relative change from baseline = treatment as fixed effect and baseline value as covariate.

The LSMEANS (± SE) relative change in visceral fat area from baseline to M12 showed that there was a statistically significantly greater decrease in visceral fat area in patients receiving rimonabant 20 mg compared with those receiving placebo at 1 year (p<0.001). Similarly, the absolute change in visceral fat area from baseline to M12 decreased in both groups, but the improvement was more marked in the rimonabant 20 mg group (-48.15 ± 4.799 cm²) than in the placebo group (-13.76 ± 4.488 cm²) with a statistically significant difference of -34.39 ± 6.574 cm² with a 95% CI from -47.35 to -21.42 cm² (p<0.001).

The same was true for the following CT-scan parameters, for which a significantly greater decrease from baseline to M12 was achieved by patients receiving rimonabant 20 mg compared with those receiving placebo: surface of total adipose tissue (-19.10 ± 1.472% versus -5.27 ± 1.423%, respectively, p<0.001), surface of subcutaneous adipose tissue (-15.97 ± 1.292% versus -5.24 ± 1.250%, respectively, p<0.001), and surface of deep subcutaneous adipose tissue (-13.96 ± 1.405% versus -4.39 ± 1.311%, respectively, p<0.001). Attenuation of liver increased in both groups, and this increase was significantly higher in patients treated with rimonabant 20 mg (33.14 ± 5.516%) than in those receiving placebo (11.03 ± 5.127%) (p=0.004). The same trend was found for the attenuation of spleen and the liver fat content (liver/spleen ratio), but with no statistically significant difference between both groups (p=0.149 and p=0.078, respectively). Ratio of surface of VAT to surface of subcutaneous adipose tissue did not change from baseline to endpoint in the placebo group (1.55 ± 2.124), while this ratio significantly decreased in the rimonabant 20 mg group (-10.14 ± 2.197) (p<0.001). A very slight decrease in the ratio of surface of VAT to surface of total adipose tissue from baseline to M12 was seen in both groups with no significant difference between rimonabant 20 mg and placebo groups (p=0.135).

The primary analysis was repeated including country or gender as fixed effect and gave similar results. When considering each gender, results were very close between males and females, except for the relative change from baseline in the attenuation of liver and the liver fat content, which were higher in males than in females in the rimonabant 20 mg group (42.08 ± 107.725% versus 26.33 ± 72.270% and 45.14 ± 119.755% versus 15.10 ± 43.284%, respectively).

In comparison to placebo, rimonabant at a dose of 20 mg induced a statistically significant reduction in body weight (ANCOVA repeated-measurements method, -9.35 ± 0.652% versus -2.61 ± 0.599%, p<0.001), and WC (ANCOVA repeated-measurements method, -8.93 ± 0.622% versus -4.31 ± 0.567%, p<0.001) at 1 year. Significant improvements in anthropometric measures were observed, particularly from V5 (M5) to V8 (M12), and appeared to be greater with the time spent. The mean weight loss appeared to be very slightly more marked in females (-9.90 ± 6.649%) than in males (-7.59 ± 5.959%) in the rimonabant 20 mg group. The same was true concerning WC (-9.01 ± 6.850% in females and -7.86± 5.823% in males).

Regarding the body composition, patients treated with rimonabant 20 mg/day achieved a reduction in total fat mass of -16.20 ± 1.307% compared to a reduction of -4.07 ± 1.215% for patients on placebo at 1 year (p<0.001). This improvement was also found for the total mass and the percentage of body fat, which were significantly reduced in the rimonabant 20 mg group than in the placebo group (p<0.001).

At 1 year, compared to the placebo, rimonabant at a dose of 20 mg resulted in a significantly greater increase in HDL-C concentration (25.12 ± 2.689% versus 6.95 ± 2.417%, p<0.001), and reduction in TG concentration from baseline (-14.37 ± 4.412% versus 1.46 ± 3.989%, p=0.008). This significant improvement in HDL-C from baseline, reported in the rimonabant 20 mg group, affected both HDL_2 (115.04 ± 25.832%) and HDL_3 subfractions (31.29 ± 4.142%). A significant increase in the LDL particle size, in the relative proportion and cholesterol concentration of large LDL particles, was also seen in the rimonabant 20 mg group (p≤0.038 versus placebo). Relative to placebo, other specific lipid parameters (total cholesterol, LDL-cholesterol, apolipoproteins) remained unchanged.

After 12 months, decrease in mean HbA_{1c} was seen in the rimonabant 20 mg group, while no change was observed in this parameter in the placebo group and the difference was statistically significant (-2.09 ± 0.604% versus 0.01 ± 0.546% respectively, p=0.011). Following an OGTT, a greater decrease in mean fasting glucose from baseline to M12 was observed in the rimonabant 20 mg group compared to the placebo group both at T0 (-0.19 ± 0.752 mmol/L versus -0.03 ± 0.528 mmol/L, respectively), and at each time-point after 30, 60 or 120 minutes. That was also true for the mean fasting insulin from baseline to 1 year (-36.46 ± 66.257 pmol/L in the rimonabant 20 mg group versus -28.85 ± 86.574 pmol/L in the placebo group at T0). After calculating the Area Under the Curve (AUC) of the glucose levels at 4 time-points (0, 30, 60, 120 minutes), the mean glucose $AUC_{0\text{-}120}$ decreased in both groups, and the difference observed in the relative change from baseline between the rimonabant 20 mg and the placebo groups was not sufficient to be significant (-6.10 ± 3.381%, p=0.074). Similar findings were observed for the mean insulin $AUC_{0\text{-}120}$ (-11.20 ± 8.002%, p=0.165). A decrease in insulin resistance assessed with Homeostasis Model Assessment (HOMA) appeared to be more marked in the rimonabant 20 mg group than in the placebo group, but with no significant difference between both groups (-13.44 ± 10.603% versus -3.68 ± 9.750%, p=0.500). The same was found for the insulin sensitivity.

Results on adipokine markers showed a statistically significantly greater decrease from baseline to M12 in leptin in favour of the rimonabant 20 mg group compared to the placebo group (-37.12 ± 3.510% versus -9.53 ± 3.169%, respectively, p<0.001). An increase from baseline to endpoint in adiponectin levels was observed in both rimonabant 20 mg (74.41 ± 5.866%) and placebo groups (36.84 ± 5.297%) with a statistically significant difference (p< 0.001).

No noticeable changes in inflammatory markers from baseline to M12 were seen between both treatment groups: a decrease from baseline in hs-CRP was observed, while an increase in the two other analyzed inflammatory markers (IL6, TNF α) was found in both treatment groups. Although the relative change from baseline to M12 appeared to be more marked in the rimonabant 20 mg group than in the placebo group for each inflammatory marker, the difference between both treatment groups was not statistically significant. In addition, no significant changes in terms of hemostatic markers (fibrinogen, PA-1) from baseline were seen in the rimonabant 20 mg group compared to the placebo group after 1 year.

At 1 year, a significantly lower proportion of patients with metabolic syndrome was observed in the rimonabant 20 mg group (50.6%) than in the placebo group (77.1%) (p<0.001). Similarly, an improvement of metabolic syndrome was observed in a higher proportion of patients under rimonabant 20 mg from baseline (40.7%) compared with those receiving placebo (16.2%) (p<0.001). Regarding each of the 5 components of the metabolic syndrome, improvement was noticed in a significant greater proportion of patients in the rimonabant 20 mg group compared to the placebo group for WC (25.5% versus 8.9%, respectively, p=0.002) and HDL-C (32.9% versus 14.4%, respectively, p=0.005) criteria.

Finally, results in the PP population were consistent with those found in the ITT population.

Safety results:

- Overview of AEs

Overall incidence of TEAEs is summarized and displayed in the following table for the safety population:

	Placebo N=129		Rimonabant 20 mg N=125		Total N=254		Test
Patients with any TEAEs (including SAEs)	110	(85.3%)	111	(88.8%)	221	(87.0%)	p=0.40*
Patients with any serious TEAEs (including SAEs leading to death)	9	(7.0%)	12	(9.6%)	21	(8.3%)	p=0.45*
Patients with any TEAEs leading to death	0	(0.0%)	0	(0.0%)	0	(0.0%)	Not applicable
Patients permanently discontinuing treatment due to TEAEs	8	(6.2%)	24	(19.2%)	32	(12.6%)	p=0.002*

[redacted]

TEAEs: defined as AEs occurred after the first intake of study drug up to 75 days following the last dose of study drug.
SOC (System Organ Class) and PT (Preferred Term) according to MedDRA 10.1 dictionary.
* Chi² test.

Of the 254 patients exposed to the study drug, 32 patients (12.6%) dropped out of the study due to TEAEs (6.2% in the placebo group versus 19.2% in the rimonabant group, p=0.002), and 21 patients (8.3%) experienced at least one SAE (7.0% in the placebo group versus 9.6% in the rimonabant group, p=0.45). No deaths occurred during the study, and 221 patients (87.0%) experienced at least one TEAE (85.3% in the placebo group versus 88.8% in the rimonabant group, p=0.40).

- Summary of TEAEs

All TEAEs are summarized by body system and by PT ≥ 4% by descending order of frequency in the following table:

TEAEs	Placebo N=129		Rimonabant 20 mg N=125		Total N=254	
All TEAEs	**110**	**(85.3%)**	**111**	**(88.8%)**	**221**	**(87.0%)**
Infections and infestations	**62**	**(48.1%)**	**55**	**(44.0%)**	**117**	**(46.1%)**
Nasopharyngitis	20	(15.5%)	21	(16.8%)	41	(16.1%)
Influenza	12	(9.3%)	11	(8.8%)	23	(9.1%)
Sinusitis	10	(7.8%)	7	(5.6%)	17	(6.7%)
Gastroenteritis	5	(3.9%)	5	(4.0%)	10	(3.9%)
Psychiatric disorders	**44**	**(34.1%)**	**58**	**(46.4%)**	**102**	**(40.2%)**
Anxiety	20	(15.5%)	33	(26.4%)	53	(20.9%)
Depressed mood	19	(14.7%)	25	(20.0%)	44	(17.3%)
Insomnia	11	(8.5%)	9	(7.2%)	20	(7.9%)
Middle insomnia	7	(5.4%)	7	(5.6%)	14	(5.5%)
Decreased interest	5	(3.9%)	6	(4.8%)	11	(4.3%)
Depression	4	(3.1%)	6	(4.8%)	10	(3.9%)
Gastrointestinal disorders	**38**	**(29.5%)**	**57**	**(45.6%)**	**95**	**(37.4%)**
Nausea	9	(7.0%)	27	(21.6%)	36	(14.2%)
Diarrhoea	9	(7.0%)	20	(16.0%)	29	(11.4%)
Vomiting	6	(4.7%)	7	(5.6%)	13	(5.1%)
Abdominal pain upper	4	(3.1%)	6	(4.8%)	10	(3.9%)
Constipation	2	(1.6%)	5	(4.0%)	7	(2.8%)

N (%): number of patients with at least one event (calculated based on the total number of patients in each treatment group in the Safety Population).
TEAEs defined as AEs occurred after the first intake of study drug up to 75 days following the last dose of study drug.
SOC and PT according to MedDRA 10.1 dictionary.

TEAEs	Placebo N=129		Rimonabant 20 mg N=125		Total N=254	
Nervous system disorders	**40**	**(31.0%)**	**55**	**(44.0%)**	**95**	**(37.4%)**
Dizziness	20	(15.5%)	27	(21.6%)	47	(18.5%)
Headache	10	(7.8%)	8	(6.4%)	18	(7.1%)
Paraesthesia	5	(3.9%)	10	(8.0%)	15	(5.9%)
Hypoaesthesia	5	(3.9%)	9	(7.2%)	14	(5.5%)
Sciatica	1	(0.8%)	6	(4.8%)	7	(2.8%)
Musculoskeletal and connective tissue disorders	**41**	**(31.8%)**	**35**	**(28.0%)**	**76**	**(29.9%)**
Arthralgia	12	(9.3%)	4	(3.2%)	16	(6.3%)
Pain in extremity	8	(6.2%)	7	(5.6%)	15	(5.9%)
Back pain	7	(5.4%)	6	(4.8%)	13	(5.1%)
Muscular weakness	2	(1.6%)	7	(5.6%)	9	(3.5%)
Myalgia	3	(2.3%)	5	(4.0%)	8	(3.1%)
General disorders and administration site conditions	**20**	**(15.5%)**	**35**	**(28.0%)**	**55**	**(21.7%)**
Asthenia	8	(6.2%)	11	(8.8%)	19	(7.5%)
Fatigue	5	(3.9%)	9	(7.2%)	14	(5.5%)
Oedema peripheral	4	(3.1%)	6	(4.8%)	10	(3.9%)
Injury, poisoning and procedural complications	**17**	**(13.2%)**	**21**	**(16.8%)**	**38**	**(15.0%)**
Fall	2	(1.6%)	5	(4.0%)	7	(2.8%)
Respiratory, thoracic and mediastinal disorders	**17**	**(13.2%)**	**16**	**(12.8%)**	**33**	**(13.0%)**
Cough	5	(3.9%)	5	(4.0%)	10	(3.9%)
Skin and subcutaneous tissue disorders	**10**	**(7.8%)**	**23**	**(18.4%)**	**33**	**(13.0%)**
Hyperhidrosis	3	(2.3%)	9	(7.2%)	12	(4.7%)
Eye disorders	**11**	**(8.5%)**	**18**	**(14.4%)**	**29**	**(11.4%)**
Metabolism and nutrition disorders	**10**	**(7.8%)**	**11**	**(8.8%)**	**21**	**(8.3%)**
Vascular disorders	**11**	**(8.5%)**	**8**	**(6.4%)**	**19**	**(7.5%)**
Reproductive system and breast disorders	**3**	**(2.3%)**	**11**	**(8.8%)**	**14**	**(5.5%)**
Cardiac disorders	**5**	**(3.9%)**	**6**	**(4.8%)**	**11**	**(4.3%)**
Ear and labyrinth disorders	**2**	**(1.6%)**	**6**	**(4.8%)**	**8**	**(3.1%)**
Investigations	**4**	**(3.1%)**	**4**	**(3.2%)**	**8**	**(3.1%)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**5**	**(3.9%)**	**2**	**(1.6%)**	**7**	**(2.8%)**
Renal and urinary disorders	**2**	**(1.6%)**	**5**	**(4.0%)**	**7**	**(2.8%)**
Blood and lymphatic system disorders	**3**	**(2.3%)**	**1**	**(0.8%)**	**4**	**(1.6%)**
Endocrine disorders	**1**	**(0.8%)**	**2**	**(1.6%)**	**3**	**(1.2%)**
Immune system disorders	**1**	**(0.8%)**	**1**	**(0.8%)**	**2**	**(0.8%)**

N (%): number of patients with at least one event (calculated based on the total number of patients in each treatment group in the Safety Population).
TEAEs defined as AEs occurred after the first intake of study drug up to 75 days following the last dose of study drug.
SOC and PT according to MedDRA 10.1 dictionary.

A total of 221 patients (87.0%) experienced at least one TEAE, i.e. 110 patients (85.3%) in the placebo group versus 111 patients (88.8%) in the rimonabant 20 mg group. The most commonly observed TEAEs by SOC were infections and infestations (46.1%), followed by psychiatric disorders (40.2%), gastrointestinal disorders (37.4%) and nervous system disorders (37.4%). The most frequently reported TEAEs by PTs were anxiety (20.9%), dizziness (18.5%), depressed mood (17.3%), nasopharyngitis (16.1%), and nausea (14.2%). In terms of TEAEs reported by SOC, infections and infestations were the most frequently observed in the placebo group (48.1%), while psychiatric disorders (46.4%) were the most commonly reported in the rimonabant 20 mg group. Psychiatric disorders (34.1% in the placebo group versus 46.4% in the rimonabant 20 mg group), gastrointestinal disorders (29.5% versus 45.6%, respectively), nervous system disorders (31.0% versus 44.0%, respectively), general disorders and administration site conditions (15.5% versus 28.0%, respectively), and skin and subcutaneous tissue disorders (7.8% versus 18.4%, respectively) were more frequently seen in patients receiving rimonabant 20 mg than in those receiving placebo. All other SOCs were well balanced in both treatment groups. In terms of TEAEs reported by PT, nasopharyngitis, anxiety, dizziness (15.5% for each) and depressed mood (14.7%) were the most commonly reported in the placebo group, while anxiety (26.4%), nausea (21.6%), dizziness (21.6%) and depressed mood (20.0%) were the most frequently observed in the rimonabant 20 mg group. The number of patients experiencing anxiety, depressed mood, nausea, diarrhoea and dizziness was higher in the rimonabant 20 mg group than in the placebo group.

The most frequent SOCs involved in permanent discontinuation due to TEAEs were: psychiatric disorders (3.1% in the placebo group and 12.0% in the rimonabant group), nervous and gastrointestinal disorders only reported in the rimonabant group (4.8% and 4.0%, respectively).

In term of TEAEs reported by PT, anxiety (2.3% in the placebo group and 4.8% in the rimonabant group) was the main reason for discontinuation due to TEAEs.

- Summary of SAEs

A total of 27 SAEs were reported in 21 patients: 12 in 9 patients (7.0%) in the placebo group compared to 15 in 12 patients (9.6%) in the rimonabant 20 mg group. The most commonly observed SAEs belonged to the following body systems: gastrointestinal disorders (1.6%), musculoskeletal and connective tissue disorders, psychiatric disorders and reproductive system and breast disorders classes (1.2% for each). The most frequently reported SAEs by PTs were gastritis and anxiety (0.8% for each). All other SAEs were occasionally reported in at least one treatment group with the same incidence of 0.4%. By SOC, musculoskeletal and connective tissue disorders, psychiatric disorders, and neoplasms benign, malignant and unspecified (1.6% for each) were the most frequently reported SAEs in the placebo group, while gastrointestinal disorders (2.4%) were the most frequently seen SAEs in the rimonabant 20 mg group. Serious anxiety occurred in 2 patients (1.6%) in the placebo group while all SAEs observed in the rimonabant 20 mg group were single cases. Finally, there were no marked differences between both treatment groups regarding the incidence of SAEs either by SOC or by PT. All SAEs are detailed in the narrative Section [redacted].

- Summary of Deaths

No deaths were reported during the study.

Conclusions: [redacted]

Date of report: 14 May 2009.