SYNOPSIS

Title of the study:	A European randomized, parallel group, two-arm placebo-controlled, double-blind multicenter study of rimonabant 20 mg once daily in the treatment of abdominally obese patients with dyslipidemia with or without other comorbidities.
Investigator:	No principal investigator.
Study centers:	The study was conducted in 99 active centers in 14 countries (Czech Republic, Finland, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Portugal, Slovakia, Sweden, Turkey and United Kingdom [UK]).
Publications (reference): None	
Study period:	
Date first patient enrolled:	06 December 2006
Date last patient completed:	30 January 2009
Phase of development:	Phase III_b/IV

Objectives:

The objectives of the protocol were as follows:

Primary:

- To determine the effect of rimonabant 20 mg on changes in HDL-Cholesterol (HDL-C), Triglyceride (TG) levels over a period of 12 months when prescribed with a mild hypocaloric diet in abdominally obese patients with dyslipidemia with or without other associated comorbidities.

Secondary:

- To determine the effect of 12 months rimonabant treatment versus placebo on changes in:
  - Waist Circumference (WC) and body weight at each visit
  - Glycemic parameters: Fasting Plasma Glucose (FPG), fasting insulinemia, Hemoglobin A_1c (HbA_1c),
  - Lipid parameters: Total Cholesterol, HDL-C, LDL-Cholesterol (LDL-C), TG levels
  - Inflammatory parameter: High Sensitivity C-Reactive Protein (Hs-CRP).
  - Quality of Life (QOL): Impact of Weight on Quality of Life (IWQOL) questionnaire completed at baseline, M3, M6, M9 and M12.
  - Blood Pressure (BP) at each visit.
- To assess the safety of 12 months rimonabant treatment versus placebo in these patients:
  - Incidence of Adverse Events (AEs) in each group, including neuro-psychiatric AEs
  - Standard laboratory assessments prior to baseline and M12.

In selected sites, a sub-study was conducted in which the following additional parameters were measured prior to baseline and M12:

- Lipid parameters: HDL subfractions, Apolipoprotein (Apo) A1, Apo A2, Apo B and Apo C3, Lipoprotein (Lp) A1, Lp A1/A2, Lp (a), Oxidized-LDL and LDL size
- Inflammatory parameters: Adiponectin-High Molecular Weight, Intracellular Adhesion Molecule 1 (ICAM-I) and Tumor Necrosis Factor alpha (TNF α).

The study was stopped prematurely due to the Sponsor's decision to discontinue the rimonabant clinical program. Consequently, the analysis (as defined in the statistical analysis plan) focused on the primary efficacy endpoint, and on a review of the safety profile based on reporting of AEs. The data which are presented in this synopsis report are also supported by limited appendices.

Methodology: This was an international phase III_b/IV, randomized [1:1], two-arm, double-blind, placebo-controlled, parallel group, fixed dose (rimonabant 20 mg once daily), multicenter study.

Number of patients:

Main Study: Planned: 876 patients Randomized: 643 patients Randomized and treated: 632 patients

Sub-Study: Planned: 380 patients

Evaluated: Safety (excluding 2 switched patients – see section "summary of populations"): 630 patients

Diagnosis and criteria for inclusion: Male or female, 18-75 years of age, with a Body Mass Index (BMI) > 27 kg/m^2 and < 40 kg/m^2 with a WC > 88 cm in women and > 102 cm in men with dyslipidemia (associated or not with comorbidities) defined as HDL-C < 40 mg/dL [1.03 mmol/L] for men and < 50 mg/dL [1.29 mmol/L] for women, and/or TG ≥ 150 mg/dL [1.69 mmol/L], and LDL-C up to 155 mg/dL [4.00 mmol/L] (including patients on a stable dose of statins and/or ezetimibe therapy for at least 8 weeks prior to screening), were considered for enrollment in the study after giving his/her written informed consent.

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

Duration of treatment: 12 months (from Day (D) 1 post-randomization to D365 ± 10)

Duration of observation: 12 months ½

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

Criteria for evaluation:

Efficacy: Efficacy criteria were as follows:

Primary:

- Mean change from baseline to end of treatment in HDL-C and TG levels.

Secondary:

- Change from baseline in:
  - WC and body weight at each visit
  - Glycemic parameters: FPG, fasting insulinemia, HbA_{1c}
  - Lipid parameters: Total Cholesterol, HDL-C, LDL-C, TG levels
  - Inflammatory parameter: Hs-CRP.

  All these laboratory parameters were measured prior to baseline, M3, M6 and M12.
  - BP at each visit.
- QOL: IWQOL questionnaire completed at baseline, M3, M6, M9 and M12.

Safety

- Incidence of AEs in each group, including neuro-psychiatric AEs
- Standard laboratory assessments prior to baseline and M12.

In selected sites, a sub-study was conducted in which additional parameters, measured prior to baseline and at M12, were as follows:

- Lipid parameters: HDL subfractions, Apo A1, Apo A2, Apo B and Apo C3, Lp A1, Lp A1/A2, Lp (a), Oxidized-LDL and LDL size
- Inflammatory parameters: Adiponectin-High Molecular Weight, ICAM-I and TNF α.

Analyses of the sub-study were not performed.

Only the primary criterion for efficacy was analyzed and reported for the main study (relative change in HDL-C and TG levels at M12 endpoint from baseline) and safety was analyzed in term of AEs.

Statistical methods:

Efficacy: All efficacy analyses were performed on Intent-To-Treat (ITT) population.

Primary efficacy analysis:

- Primary analysis of the primary efficacy variables

The relative change from baseline to M12 endpoint in HDL-C and TG were compared between treatment groups using separate student T-tests. In order to control the type I error, a level of 0.025 was used for each of the two p-values observed. If one of them was significant, then, the global test for the primary endpoint was considered as significant.

Baseline and M12 endpoint values were also summarized by treatment group using descriptive statistics. M12 endpoint was defined as the last available value following the first dose of study drug up to the end of the treatment period; only laboratory data performed within the 14 days after the date of last dose were used.

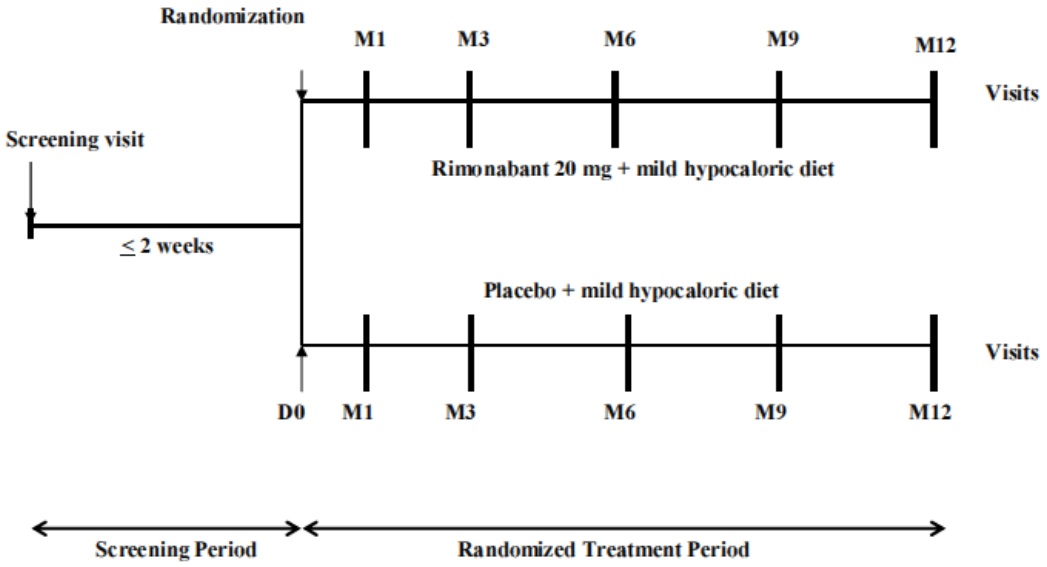
Secondary efficacy analyses: Secondary efficacy parameters were not analyzed.

Safety: Safety analyses were carried out on the safety population. Treatment Emergent Adverse Events (TEAEs) were summarized by treatment group using descriptive statistics, and the incidence of TEAEs was compared between treatment groups using a Chi^2 test. Other safety variables included pre- and post-treatment AEs.

Details on statistical methods are given in the statistical analysis plan.

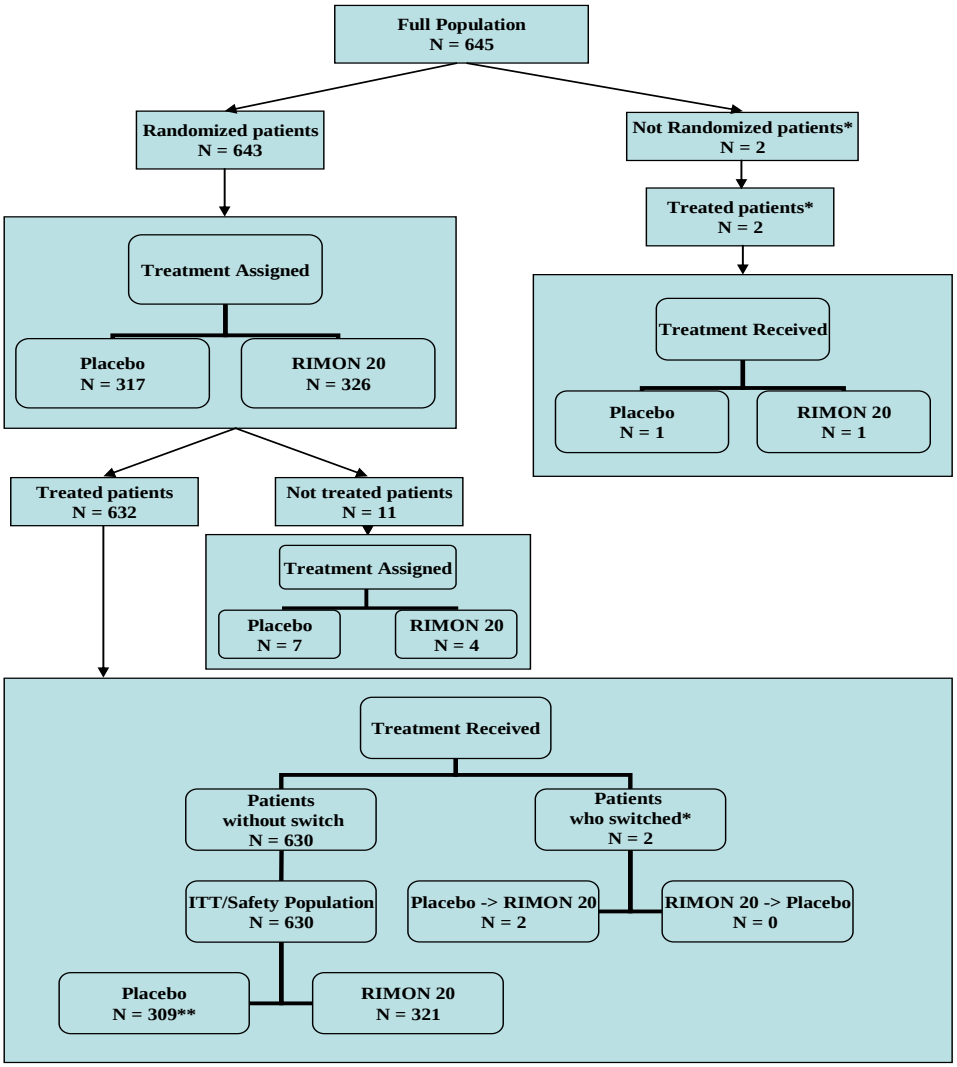
Summary:

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:

The disposition of patients who were randomized is outlined in the following flow-chart and table:



* Patients who were treated (but not randomized), and those who switched during the study were excluded from statistical analyses, but were described separately in tabulated summaries (see Appendix 14.4.2):
- Two patients were treated but not randomized (IVRS not called): 1 (placebo), (rimonabant 20 mg).
- Two patients switched (first treatment received presented): and (placebo for each).

** Patient with treatment assigned = rimonabant 20 mg, treatment received = placebo.

Eleven patients were randomized and not treated:

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Populations	Placebo N=317		Rimonabant 20 mg N=326		Total N=643	
Randomized population	317	(100.0%)	326	(100.0%)	643	(100.0%)
ITT population*	309	(97.5%)	321	(98.5%)	630	(98.0%)
Safety population*	309	(97.5%)	321	(98.5%)	630	(98.0%)

Randomized population: all patients for whom the Interactive Voice Response System (IVRS) was called (before the first intake of the study drug) and for whom an IVRS number was allocated following the phone contact.
ITT population: all randomized patients who received at least one dose (tablet) of the study drug (patient in switch not included).
Safety population: all randomized patients who received at least one dose (tablet) of the study drug (patient in switch not included).
* According to treatment received.
Patient # 276105001 with treatment assigned = rimonabant 20 mg, treatment received = placebo.

Patient disposition:

Overall, 417 randomized patients (66.2%), 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=309		Rimonabant 20 mg N=321		Total N=630	
All withdrawals	202	(65.4%)	215	(67.0%)	417	(66.2%)
AE	17	(5.5%)	35	(10.9%)	52	(8.3%)
Poor compliance to protocol	3	(1.0%)	3	(0.9%)	6	(1.0%)
Subject's request	20	(6.5%)	16	(5.0%)	36	(5.7%)
Subject lost to follow-up	7	(2.3%)	6	(1.9%)	13	(2.1%)
Other reason: sponsor request*	152	(49.2%)	152	(47.4%)	304	(48.3%)
Other reason than sponsor request	3	(1.0%)	3	(0.9%)	6	(1.0%)

* Due to the discontinuation of the rimonabant clinical program.

Sponsor request (48.3%) was the most frequent reason reported in both treatment groups (49.2% in the placebo group and 47.4% in the rimonabant 20 mg group). The next most common reason was the occurrence of AE (8.3%) which occurred more frequently in the rimonabant 20 mg group (10.9%) than in the placebo group (5.5%). Other withdrawals were due to the subject's request (5.7%), lost to follow-up (2.1%), poor compliance to the protocol (1.0%) and other reason than sponsor request (1.0%), and were comparable between both treatment groups.

Exposure:

Extent of exposure was summarized on the safety population in each treatment group as follows:

Extent of exposure	Placebo N=309	Rimonabant 20 mg N=321	Total N=630
Duration of exposure* (days)			
N	309	321	630
Mean (SD)	228.7 (126.43)	223.3 (127.06)	226.0 (126.68)
Median	229.0	222.0	225.0
Min/Max	1 / 398	3 / 391	1 / 398
Duration of exposure* classes (days)			
[1 - 30]	22 (7.1%)	22 (6.9%)	44 (7.0%)
[31 - 90]	35 (11.3%)	46 (14.3%)	81 (12.9%)
[91 - 180]	64 (20.7%)	58 (18.1%)	122 (19.4%)
[181 - 270]	57 (18.4%)	59 (18.4%)	116 (18.4%)
[271 - 364]	78 (25.2%)	84 (26.2%)	162 (25.7%)
> 364	53 (17.2%)	52 (16.2%)	105 (16.7%)

SD: Standard Deviation

* 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 or incomplete date of first dose, the date of randomization (from IVRS) was used.
If only the day of the last dose was unknown (month and year fully completed), the day had to be replaced by the last day of the month.
In case of missing date or incomplete date of last dose (except when day only was unknown), the date of the last study drug dispensing, or the date of the last visit when the last study drug dispensing date was unknown, was used. This rule (using the date of last dose dispensed) allowed assessing the minimum duration of exposure, especially for patients lost to follow up)

The mean duration of exposure was similar in both treatment groups (228.7 ± 126.43 days in the placebo group versus 223.3 ± 127.06 days in the rimonabant 20 mg group). The duration of exposure ranged from 181 days to more than 364 days for approximately two thirds of patients (60.8%).

Demographics:

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

Demographics	Placebo N=309	Rimonabant 20 mg N=321	Total N=630
Age* (years)			
Mean (SD)	51.6 (12.01)	51.2 (11.57)	51.4 (11.78)
Median	52.0	52.0	52.0
Min/Max	20 / 75	19 / 75	19 / 75
Gender (n, %)			
Males	162 (52.4%)	152 (47.4%)	314 (49.8%)
Females	147 (47.6%)	169 (52.6%)	316 (50.2%)
Ethnic origin (n, %)			
Caucasian	304 (98.4%)	320 (99.7%)	624 (99.0%)
Black	1 (0.3%)	0 (0.0%)	1 (0.2%)
Asian/oriental	2 (0.6%)	0 (0.0%)	2 (0.3%)
Other	2 (0.6%)	1 (0.3%)	3 (0.5%)
BMI (kg/m²)**			
Mean (SD)	34.13 (3.65)	33.47 (3.60)	33.79 (3.64)
Median	33.80	33.20	33.50
Min/Max	26.5 / 43.7	26.8 / 40.9	26.5 / 43.7
WC (cm)			
Mean (SD)	112.38 (10.15)	111.24 (11.24)	111.80 (10.73)
Median	111.00	111.00	111.00
Min/Max	87.5 / 147.0	88.4 / 180.0	87.5 / 180.0

* Age in years calculated as integer (date of Visit 1 [V1] - date of birth)/ 365.25.
** BMI in kg/m² calculated as weight in kg/(height in m)² rounded up to one decimal place.

The safety population was almost equally distributed between males (49.8%) and females (50.2%). The majority of patients were Caucasian (99.0%). All demographic and baseline characteristics were similar in both treatment groups except for gender. A slightly higher proportion of male patients was observed in the placebo group (52.4%) compared with the rimonabant 20 mg group (47.4%). The mean patient age was 51.4 ± 11.78 years. The mean BMI was 33.79 ± 3.64 kg/m² with a range of [26.5 - 43.7] kg/m². The mean WC was 111.80 ± 10.73 cm with a range of [87.5-180.0] cm.

Efficacy results:

Results of the co-primary efficacy endpoints in the ITT population are presented in the following tables:

- Relative change in HDL-C from baseline to the end of treatment (M12 endpoint):

HDL-C	Placebo N=309	Rimonabant 20 mg N=321	Student T-Test
N* (missing)	266 (43)	290 (31)	
Baseline (mmol/L)			
Mean (SD)	1.00 (0.20)	1.02 (0.22)	
Median	0.97	0.99	
Min/Max	0.13 / 1.68	0.42 / 1.96	
M12 endpoint (mmol/L)			
Mean (SD)	1.02 (0.21)	1.14 (0.28)	
Median	0.98	1.11	
Min/Max	0.39 / 1.82	0.53 / 2.50	
Relative Change from Baseline (%)			
Mean (SD)	3.83 (42.63)	11.32 (17.44)	p = 0.008
Median	0.00	8.50	
Min/Max	-36.07 / 661.54	-31.76 / 82.42	

N*: patients available for the change from baseline.

The mean (± SD) relative change in HDL-C levels from baseline to end of treatment showed that there was a statistically significantly greater increase in HDL levels in patients receiving rimonabant 20 mg compared with those receiving placebo (11.32 ± 17.44% versus 3.83 ± 42.63%, p=0.008).

- Relative change in TG from baseline to the end of treatment (M12 endpoint):

TG	Placebo N=309	Rimonabant 20 mg N=321	Student T-Test
N* (missing)	267 (42)	290 (31)	
Baseline (mmol/L)			
Mean (SD)	2.51 (0.78)	2.50 (0.75)	
Median	2.37	2.35	
Min/Max	0.74 / 4.48	0.62 / 4.46	
M12 endpoint (mmol/L)			
Mean (SD)	2.65 (1.29)	2.17 (1.00)	
Median	2.42	1.91	
Min/Max	0.73 / 10.39	0.56 / 6.33	
Relative Change from Baseline (%)			
Mean (SD)	8.60 (46.26)	-10.73 (38.36)	p < 0.001
Median	0.00	-16.63	
Min/Max	-66.50 / 280.59	-71.14 / 268.14	

N*: patients available for the change from baseline.

At the end of treatment, the mean relative change from baseline was statistically different between treatment groups in favour of rimonabant 20mg with a decrease of 10.73 ± 38.36% versus an increase of 8.60 ± 46.26% in the placebo group,(p< 0.001).

As at least one of student p-values was significant at level 0.025, then, the global test for the primary endpoint was considered as significant.

Safety results:

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

	Placebo N=309	Rimonabant 20 mg N=321	Test*
Patients with any TEAEs (including SAEs)	157 (50.8%)	176 (54.8%)	p=0.31*
Patients with any serious TEAEs (including SAEs leading to death)	20 (6.5%)	20 (6.2%)	p=0.90*
Patients with any TEAEs leading to death	1 (0.3%)	0 (0.0%)	Not applicable
Patients permanently discontinuing treatment due to TEAEs	17 (5.5%)	35 (10.9%)	p=0.014*

N (%): number of patients with at least one event.
TEAEs defined as AEs developed or worsened (according to the investigator opinion) or became serious after the first dose of the study drug up to 75 days (5 x half life) following the last dose of study drug.
SAEs: Serious Adverse Events
* Chi² test.

TEAEs occurred in a similar proportion of patients in each treatment group (157 patients [50.8%] in the placebo group versus 176 patients [54.8%] in the rimonabant 20 mg group, p=0.31). The same was true for SAEs (20 patients [6.5%] in the placebo group versus 20 patients [6.2%] in the rimonabant 20 mg group, p=0.90). One death (0.3%) occurred in the placebo group during the study. A higher proportion of patients in the rimonabant 20 mg group than in the placebo group dropped out of the study due to TEAEs (35 patients [10.9%] versus 17 patients [5.5%], respectively, p=0.014)

- Summary of TEAEs

A total of 157 patients (50.8%) in the placebo group versus 176 patients (54.8%) in the rimonabant 20 mg group experienced at least one TEAE.

In terms of TEAEs reported by SOC, gastrointestinal disorders (12.0% in the placebo group versus 19.9% in the rimonabant 20 mg group), psychiatric disorders (11.3% versus 18.4%, respectively), and nervous system disorders (9.7% versus 16.5%, 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.

TEAEs are presented in the following table by PT ≥ 4% in at least one treatment group by decreasing frequency in the rimonabant 20 mg group:

TEAEs	Placebo N=309		Rimonabant 20 mg N=321	
All TEAEs	**157**	**(50.8%)**	**176**	**(54.8%)**
Nausea	6	(1.9%)	25	(7.8%)
Dizziness	7	(2.3%)	18	(5.6%)
Depressed mood	9	(2.9%)	16	(5.0%)
Anxiety	4	(1.3%)	15	(4.7%)
Depression	5	(1.6%)	15	(4.7%)
Headache	9	(2.9%)	15	(4.7%)
Diarrhoea	9	(2.9%)	14	(4.4%)
Hyperhidrosis	8	(2.6%)	13	(4.0%)
Nasopharyngitis	14	(4.5%)	11	(3.4%)

% of subjects was calculated based on the total number of patients in each treatment group in the Safety Population.
TEAEs defined as AEs developed or worsened (according to the investigator opinion) or became serious after the first dose of the study drug up to 75 days (5 x half life) following the last dose of study drug.
PT according to MedDRA 10.1 dictionary.
TEAEs more frequent (≥4%) defined as TEAEs with a frequency ≥4% in at least one treatment group.

In terms of TEAEs reported by PT, nasopharyngitis (4.5%), headache, diarrhoea and depressed mood (2.9% for each), and hyperhidrosis (2.6%) were the most frequently reported in the placebo group, while nausea (7.8%), dizziness (5.6%), depressed mood (5.0%), and anxiety, depression and headache (4.7% for each) were the most commonly reported in the rimonabant 20 mg group. The number of patients experiencing nausea was higher in the rimonabant 20 mg group (7.8%) than in the placebo group (1.9%).

The most frequent SOCs involved in permanent discontinuation due to TEAEs were psychiatric disorders in both treatment groups (3.2% in the placebo group versus 6.5% in the rimonabant 20 mg group), followed by gastrointestinal disorders (1.0% versus 3.1%, respectively) and nervous system disorders (0.6% versus 1.9%, respectively).

In terms of TEAEs reported by PT, depressed mood and depression were the main reasons for discontinuation due to TEAEs in the placebo group with the same incidence of 1.0%, while depression and nausea were mostly reported in the rimonabant 20 mg group (2.5% and 2.2%, respectively).

- Summary of SAEs

SAEs occurred in a similar proportion of patients in each treatment group: 20 patients (6.5%) in the placebo group and 20 patients (6.2%) in the rimonabant 20 mg group. The most frequently observed SAEs belonged to the following body systems: cardiac disorders (1.6%) in each treatment group, psychiatric disorders (1.6%) in the rimonabant 20 mg group and (0.6%) in the placebo group, and infections and infestations (1.3%) in the placebo group and (0.6%) in the rimonabant 20 mg group. By PT, serious angina pectoris and angina unstable were reported in 3 patients (1.0%) and 2 patients (0.6%) in the placebo group, respectively. Serious depression (3 patients, 0.9%), diverticulitis and angina pectoris (2 patients, 0.6% for each) were the most commonly reported SAEs in the rimonabant 20 mg group. All other SAEs observed in each treatment group were single cases. Regarding serious psychiatric disorders observed in the rimonabant 20 mg group, three patients experienced moderate depression, one patient experienced severe major depression, and another patient experienced moderate aggressiveness. Of them, study treatment was discontinued for three patients, and all recovered without sequelae. Tabulated narratives for all SAEs are provided in the narrative section of the CSR.

- Summary of Deaths

One death (sudden cardiac death in one patient) was reported in the placebo group during the study. This case is detailed in the narrative section of the CSR.

Conclusions: [redacted]

Date of report: 29 July 2009.