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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis **Drug substance(s):** Rimonabant	**Study Identifier:** NCT00405808 **Study code:** RIMON_R_00961
Title of the study: A Pan-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 impaired fasting blood glucose with or without other comorbidities.	
Study centers: The study was conducted in 318 active centers in 25 countries (Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Denmark, Finland, France, Greece, Hungary, Ireland, Israel, Italy, Lithuania, Mexico, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, Turkey, and United Kingdom [UK]).	
Publications (reference): None	
Study period: Date first patient enrolled: 18 December 2006 Date last patient completed: 04 February 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 the co-primary endpoints including Fasting Plasma Glucose (FPG), HDL-Cholesterol (HDL-C) and Triglyceride (TG) levels over a period of 12 months when prescribed with a mild hypocaloric diet in abdominally obese patients with impaired fasting blood glucose and with or without 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: 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.

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.

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:

Planned: 4830 patients Randomized: 2663 patients Randomized and treated: 2637 patients

Evaluated: Safety (excluding 6 switched patients, *see Section "Summary of populations"*): 2631 patients

Diagnosis and criteria for inclusion:
- Male or female, 18-75 years of age,
- with a Body Mass index (BMI):
  - ≥ 30 kg/m^2
  - **or** > 27 kg/m^2 if associated with risk factor(s) such as:
    - Dyslipidemia and < 40 kg/m^2,
    - with a WC > 88 cm in women and > 102 cm in men,
    - and with confirmed impaired FPG defined as FPG ≥ 100 mg/dL [5.6 mmol/L] and < 126 mg/dL [7.0 mmol/L] on at least 2 occasions,
    - 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.

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

Duration of observation: 12 months 1/2

Reference therapy: Placebo (identical in appearance to the rimonabant tablets), oral administration, once a day, in the morning before breakfast.

Criteria for evaluation:

Efficacy: Efficacy criteria were as follows:

Primary:

- Mean change from baseline to end of treatment in the co-primary endpoints: FPG, 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

Only the primary efficacy variables, including a set of three co-primary endpoints, were analyzed and reported for the study: relative change in HDL-C and TG levels, and absolute change in FPG between end of treatment (M12 endpoint) and baseline. 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, and absolute change from baseline to M12 endpoint in FPG were compared between treatment groups using separate student T-tests.

In order to control the type I error, a level of 0.0167 was used for each of the three p-values observed. If one of them was significant, then, the global test for the primary endpoint was considered as significant.

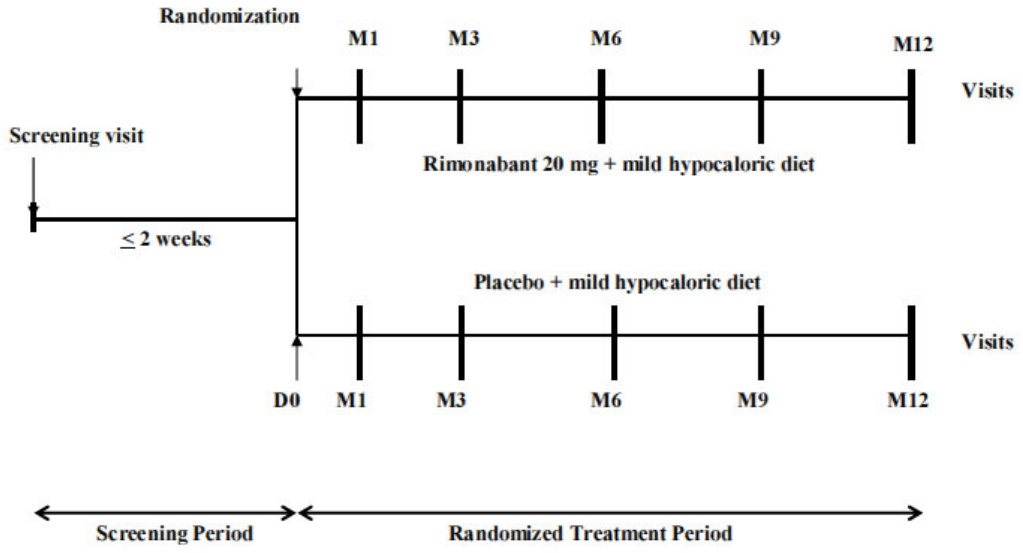
Baseline and M12 endpoint values were also summarized by treatment group using descriptive statistics. M12 endpoint was defined as the last available value following the first dose of study drug up to the end of the treatment period; only laboratory data performed within the 14 days after the date of 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 each treatment group using a Chi^2 test. Other safety variables included pre- and post-treatment AEs.

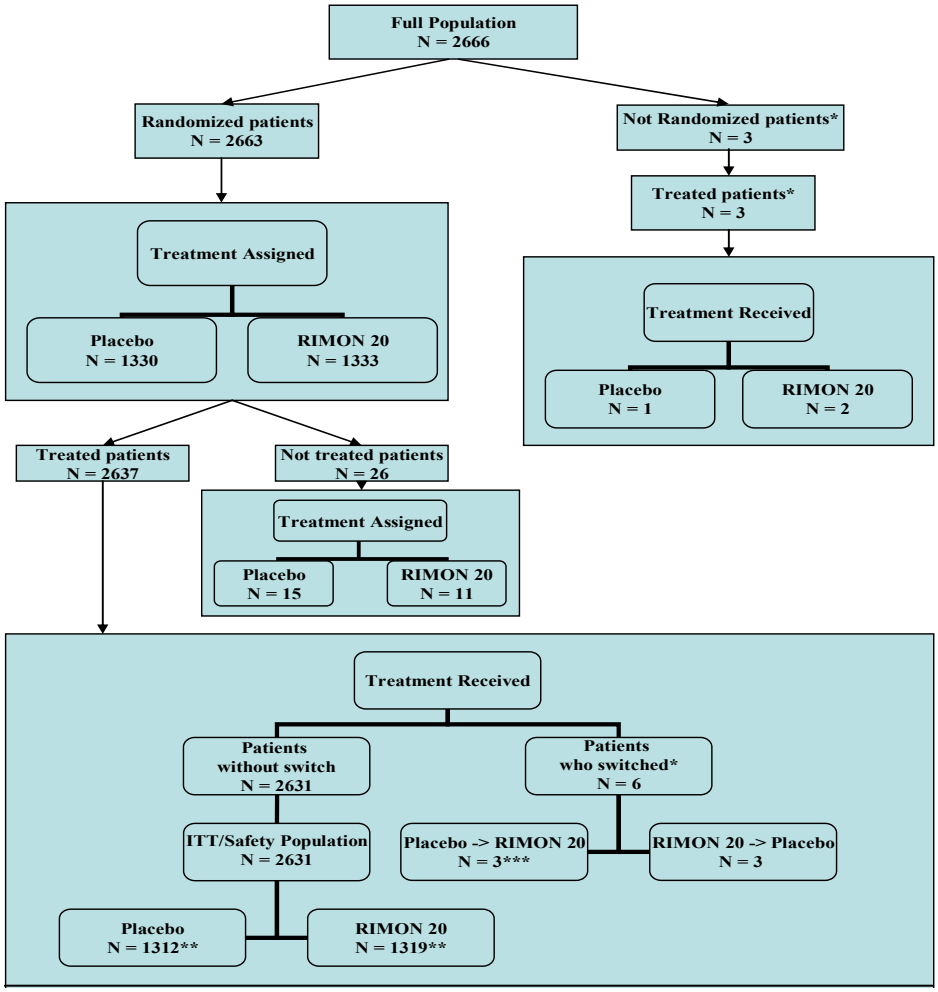
Summary:

A summary of the study design is provided below.



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.
- Three patients were treated but not randomized (IVRS not called): one patient with placebo, two patients with rimonabant 20 mg.
- Six patients switched (first treatment received presented: 3 with placebo, 3 with rimonabant 20 mg), ie patients who have been treated with both treatments by mistake during the study.

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

*** One patient took placebo, rimonabant 20 mg and placebo.

Twenty-six patients were not treated.

Populations	Placebo N=1330		Rimonabant 20 mg N=1333		Total N=2663	
Randomized population	1330	(100.0%)	1333	(100.0%)	2663	(100.0%)
ITT population*	1312	(98.6%)	1319	(98.9%)	2631	(98.8%)
Safety population*	1312	(98.6%)	1319	(98.9%)	2631	(98.8%)

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).

Patient disposition:

Overall, 1507 randomized patients (57.3%), 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=1312		Rimonabant 20 mg N=1319		Total N=2631	
All withdrawals	720	(54.9%)	787	(59.7%)	1507	(57.3%)
AE	89*	(6.8%)	217	(16.5%)	306*	(11.6%)
Poor compliance to protocol	8	(0.6%)	12	(0.9%)	20	(0.8%)
Subject's request	98	(7.5%)	60	(4.5%)	158	(6.0%)
Subject lost to follow-up	25	(1.9%)	20	(1.5%)	45	(1.7%)
Other reason: sponsor request**	457	(34.8%)	444	(33.7%)	901	(34.2%)
Other reason than sponsor request	43	(3.3%)	34	(2.6%)	77	(2.9%)

* Three patients in the placebo group were withdrawn due to pre-treatment adverse event (not TEAE).

** Due to the discontinuation of the rimonabant clinical program.

Sponsor request, due to the discontinuation of the rimonabant clinical program, (34.2%) was the most frequent reason reported in both treatment groups (34.8% in the placebo group and 33.7% in the rimonabant 20 mg group). The next most common reason was the occurrence of AE (11.6%) which occurred more frequently in the rimonabant 20 mg group (16.5%) than in the placebo group (6.8%). Other withdrawals were due to the subject's request (6.0%), other reason than sponsor request (2.9%), lost to follow-up (1.7%), poor compliance to the protocol (0.8%) and were comparable between both treatment groups except subject request (more frequent in placebo group (7.5% versus 4.5%)).

Exposure:

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

Extent of exposure	Placebo N=1312		Rimonabant 20 mg N=1319		Total N=2631	
Duration of exposure* (days)						
N	1312		1319		2631	
Mean (SD)	260.8 (122.55)		246.6 (127.73)		253.7 (125.35)	
Median	323.0		288.0		315.0	
Min/Max	1 / 469		1 / 420		1 / 469	
Duration of exposure* classes (days)						
[1 - 30]	78	(5.9%)	93	(7.1%)	171	(6.5%)
[31 - 90]	114	(8.7%)	152	(11.5%)	266	(10.1%)
[91 - 180]	177	(13.5%)	191	(14.5%)	368	(14.0%)
[181 - 270]	180	(13.7%)	183	(13.9%)	363	(13.8%)
[271 - 364]	483	(36.8%)	441	(33.4%)	924	(35.1%)
> 364	280	(21.3%)	259	(19.6%)	539	(20.5%)

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 (260.8 ± 122.55 days in the placebo group versus 246.6 ± 127.73 days in the rimonabant 20 mg group). The duration of exposure ranged from 271 days to more than 364 days for approximately half of patients (55.6%).

Demographics:

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

Demographics	Placebo N=1312	Rimonabant 20 mg N=1319	Total N=2631
Age* (years)			
Mean (SD)	54.3 (10.84)	54.6 (11.17)	54.5 (11.00)
Median	55.0	56.0	56.0
Min/Max	18 / 80	20 / 75	18 / 80
Gender (n, %)			
Males	553 (42.1%)	507 (38.4%)	1060 (40.3%)
Females	759 (57.9%)	812 (61.6%)	1571 (59.7%)
Ethnic origin (n, %)			
Caucasian	1097 (83.6%)	1113 (84.4%)	2210 (84.0%)
Black	19 (1.4%)	22 (1.7%)	41 (1.6%)
Asian/oriental	11 (0.8%)	11 (0.8%)	22 (0.8%)
Other	185 (14.1%)	173 (13.1%)	358 (13.6%)
BMI (kg/m^2)**			
N (missing)	1311 (1)	1318 (1)	2629 (2)
Mean (SD)	33.99 (3.76)	34.02 (3.68)	34.01 (3.72)
Median	33.60	33.80	33.70
Min/Max	23.0 / 57.5	24.8 / 50.6	23.0 / 57.5
WC (cm)			
Mean (SD)	109.53 (10.08)	109.47 (10.37)	109.50 (10.23)
Median	108.90	108.50	108.70
Min/Max	82.7 / 154.7	84.0 / 159.7	82.7 / 159.7

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

** BMI in kg/m^2 calculated as weight in kg/(height in m)^2 rounded up to one decimal place.

The majority of patients were female (59.7%) and Caucasian (84.0%). All demographic and baseline characteristics were similar in both treatment groups. The mean patient age was 54.5 ± 11.00 years. The mean BMI was 34.01 ± 3.72 kg/m^2 with a range of [23.0 – 57.5] kg/m^2. The mean WC was 109.50 ± 10.23 cm with a range of [82.7-159.7] cm.

Efficacy results:

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

- Absolute change in FPG from baseline to the end of treatment (M12 endpoint):

FPG	Placebo N=1312	Rimonabant 20 mg N=1319	Student T-Test
N* (missing)	1189 (123)	1164 (155)	
Baseline (mmol/L)			
Mean (SD)	6.18 (0.38)	6.21 (0.38)	
Median	6.20	6.20	
Min/Max	5.4 / 8.0	5.0 / 7.5	
M12 endpoint (mmol/L)			
Mean (SD)	6.21 (0.80)	6.08 (0.70)	
Median	6.10	6.00	
Min/Max	3.9 / 11.6	4.2 / 13.1	
Absolute Change from Baseline (mmol/L)			
Mean (SD)	0.03 (0.75)	-0.13 (0.66)	p < 0.001
Median	0.00	-0.20	
Min/Max	-2.7 / 4.7	-2.3 / 7.0	

N*: patients available for the change from baseline.

The mean absolute change in FPG from baseline to end of treatment decreased in the rimonabant 20 mg group, while no change was observed in this parameter in the placebo group, and the difference was statistically significant (-0.13 ± 0.66 mmol/L versus 0.03 ± 0.75 mmol/L, p < 0.001).

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

HDL-C	Placebo N=1312	Rimonabant 20 mg N=1319	Student T-Test
N* (missing)	1190 (122)	1171 (148)	
Baseline (mmol/L)			
Mean (SD)	1.29 (0.33)	1.30 (0.34)	
Median	1.24	1.25	
Min/Max	0.53 / 3.06	0.51 / 3.09	
M12 endpoint (mmol/L)			
Mean (SD)	1.28 (0.34)	1.38 (0.37)	
Median	1.23	1.33	
Min/Max	0.44 / 3.07	0.53 / 3.15	
Relative Change from Baseline (%)			
Mean (SD)	0.07 (14.82)	7.94 (18.16)	p < 0.001
Median	-0.78	6.36	
Min/Max	-41.33 / 107.29	-48.74 / 235.29	

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 (7.94 ± 18.16% versus 0.07 ± 14.82%, p < 0.001).

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

TG	Placebo N=1312	Rimonabant 20 mg N=1319	Student T-Test
N* (missing)	1170 (142)	1156 (163)	
Baseline (mmol/L)			
Mean (SD)	1.67 (0.77)	1.70 (0.77)	
Median	1.50	1.54	
Min/Max	0.46 / 5.63	0.42 / 5.19	
M12 endpoint (mmol/L)			
Mean (SD)	1.67 (0.88)	1.53 (0.83)	
Median	1.48	1.34	
Min/Max	0.40 / 10.28	0.36 / 8.03	
Relative Change from Baseline (%)			
Mean (SD)	5.67 (41.28)	-5.19 (38.99)	p < 0.001
Median	-1.88	-11.46	
Min/Max	-72.29 / 281.61	-73.39 / 535.20	

N*: patients available for the change from baseline.

At the end of treatment, compared to the placebo, rimonabant at a dose of 20 mg resulted in a significantly greater reduction in TG levels from baseline (-5.19 ± 38.99% versus 5.67 ± 41.28%, p< 0.001).

As at least one of student p-values was significant at level 0.0167, 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=1312		Rimonabant 20 mg N=1319		Test
Patients with any TEAEs (including SAEs)	733	(55.9%)	838	(63.5%)	p < 0.001*
Patients with any serious TEAEs (including SAEs leading to death)	68	(5.2%)	65	(4.9%)	p = 0.77*
Patients with any TEAEs leading to death	0	(0.0%)	1	(0.1%)	Not applicable
Patients permanently discontinuing treatment due to TEAEs	86	(6.6%)	217	(16.5%)	p < 0.001*

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.

A higher proportion of patients in the rimonabant 20 mg group than in the placebo group dropped out of the study due to TEAEs (217 patients [16.5%] versus 86 patients [6.6%], respectively, p<0.001). Similarly, more patients in the rimonabant 20 mg group than in the placebo group experienced at least one TEAE (838 patients [63.5%] versus 733 patients [55.9%], respectively, p < 0.001). SAEs occurred in a similar proportion of patients in each treatment group (68 patients [5.2%] in the placebo group versus 65 patients [4.9%] in the rimonabant 20 mg group, p = 0.77). One death (0.1%) occurred in the rimonabant 20 mg group during the study.

- Summary of TEAEs

A total of 733 patients (55.9%) in the placebo group versus 838 patients (63.5%) in the rimonabant 20 mg group experienced at least one TEAE.

In terms of TEAEs reported by System Organ Class (SOC), psychiatric disorders (14.2% in the placebo group versus 24.3% in the rimonabant 20 mg group), gastrointestinal disorders (13.6% versus 21.0%, respectively), nervous system disorders (14.4% versus 18.3%, respectively), and general disorders and administration site conditions (6.5% versus 10.8%, respectively) were more frequently seen in patients receiving rimonabant 20 mg than in those receiving placebo. Overall, all other SOCs were well balanced in both treatment groups.

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

TEAEs	Placebo N=1312		Rimonabant 20 mg N=1319	
Nausea	34	(2.6%)	146	(11.1%)
Dizziness	79	(6.0%)	111	(8.4%)
Anxiety	65	(5.0%)	109	(8.3%)
Depressed mood	47	(3.6%)	79	(6.0%)
Diarrhoea	36	(2.7%)	69	(5.2%)
Insomnia	40	(3.0%)	64	(4.9%)
Depression	25	(1.9%)	61	(4.6%)
Nasopharyngitis	58	(4.4%)	48	(3.6%)

% 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.

In terms of TEAEs reported by PT, dizziness (6.0%), anxiety (5.0%), and nasopharyngitis (4.4%) were the most frequently reported in the placebo group, while nausea (11.1%), dizziness (8.4%), anxiety (8.3%), depressed mood (6.0%), diarrhoea (5.2%), insomnia (4.9%), and depression (4.6%) were the most commonly observed in the rimonabant 20 mg group. The

number of patients experiencing nausea was higher in the rimonabant 20 mg group (11.1%) than in the placebo group (2.6%).

Regarding psychiatric disorders, anxiety (5.0% in the placebo group versus 8.3% in the rimonabant 20 mg group), depressed mood (3.6% versus 6.0%, respectively), insomnia (3.0% versus 4.9%, respectively) and depression (1.9% versus 4.6%, respectively) were the most frequent in each treatment group. In addition, seven cases of suicidal ideation were reported in both treatment groups (3 patients in the placebo group, 4 patients in the rimonabant 20 mg group), six cases of major depression were observed in the rimonabant 20 mg group and none in placebo group, and one case of suicide attempt was notified in the placebo group.

In both treatment groups, the most frequent SOCs involved in permanent discontinuation due to TEAEs were psychiatric disorders (3.0% in the placebo group versus 10.2% in the rimonabant 20 mg group), gastrointestinal disorders (1.2% versus 3.4%, respectively) and nervous system disorders (1.4% versus 2.7%, respectively).

In terms of TEAEs reported by PT, depression was the main reason for discontinuation due to TEAEs in both treatment groups (1.1% in the placebo group versus 3.0% in the rimonabant 20 mg group), followed by anxiety (0.7% versus 2.4%, respectively). The next most commonly reported TEAEs were nausea (2.2%) and dizziness (1.4%) in the rimonabant 20 mg group.

- Summary of SAEs

SAEs occurred in a similar proportion of patients in each treatment group: 68 patients (5.2%) in the placebo group and 65 patients (4.9%) in the rimonabant 20 mg group. The most frequently observed SAEs belonged to the following body systems: psychiatric disorders (1.3%) in the rimonabant 20 mg group and cardiac disorders in each treatment group with the same incidence of 0.8%. By PT, the most frequently SAEs observed in the placebo group were depression, osteoarthritis and myocardial infarction each reported in 3 patients (0.2%) in the placebo group. Depression (6 patients, 0.5%) and suicidal ideation (4 patients, 0.3%) were the most commonly observed SAEs in the rimonabant 20 mg group. All other SAEs observed in each treatment group were experienced by either one or two patients.

Regarding the 7 cases of suicidal ideation mentioned above, 6 cases were considered serious. The remaining patient experienced non-serious suicidal ideation and anxiety disorders associated with a depression reported as serious. All serious cases of suicidal ideation were mainly mild to moderate, except for 3 severe cases (1 patient in the placebo group and 2 patients in the rimonabant 20 mg group). In all serious cases, the study treatment was discontinued, and patients recovered. The serious case of suicide attempt, observed in the only one patient receiving placebo, was rated severe. This patient also suffered from depression reported as serious and experienced cardiac arrest due to suicidal attempt with opioid drugs. A corrective treatment was administered and the patient recovered without sequelae.

A total of 5 post-treatment SAEs were reported in 3 patients (0.2%) in the rimonabant 20 mg group.

- Summary of Deaths

One death following a peritonitis complicated in sepsis was reported in the rimonabant 20 mg group during the overall study.

Date of report: 7 September 2009.