SYNOPSIS

Title of the study:	A 12-month multicentre, randomised, double-blind, placebo-controlled study with two parallel groups to assess the effects of rimonabant 20 mg in patients with abdominal obesity and microalbuminuria, with type 2 diabetes mellitus or dyslipidaemia with or without other cardiometabolic risk factors.	
Investigator(s):	[redacted]	
Study center(s):	[redacted]	
Publications (reference):		
Study period: Date first patient enrolled: 12/03/2007 Date last patient completed: 29/01/2009		**Phase of development:** Phase IIIB
Objectives:	Primary objective: To assess the effect on microalbuminuria levels of treatment with rimonabant 20 mg versus a placebo during a 12 month period. The treatment was administered in conjunction with a slightly reduced calorie diet to patients with abdominal obesity, with type 2 diabetes mellitus or dyslipidaemia, with or without other cardiometabolic risk factors. This parameter was measured at baseline visit and at 3, 6 and 12 months. Secondary objectives: Percentage of patients in both arms of the study whose levels of microalbuminuria decrease, stabilise, increase towards macroalbuminuria or are unchanged after 12 months of treatment with rimonabant or placebo. To assess the effect of treatment with rimonabant 20 mg versus placebo over a 12 month period on: Anthropometric Variables (weight and waist circumference). Glycaemia profile: fasting glycaemia, fasting insulinaemia and HbA1c. Lipid and lipoprotein profile: triglycerides, total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), apolipoproteins A1 and B. Inflammatory markers: high-sensitivity C-reactive protein (hs-CRP), IL-6, TNF-α.	

	Adipocytokines: adiponectin. Blood pressure. Glomerular filtration rate. All these parameters were measured at baseline visit and at 3, 6 and 12 months, with the exception of the apolipoproteins, IL-6 and TNF-α which were only determined at the baseline visit and at 12 months. To assess the quality of life: questionnaire Impact of Weight on Quality of Life (IWQOL) was completed at baseline visit and at 3, 6, and 12 months. Safety parameters: - Incidence of adverse events (AEs) in each group, including neuropsychiatric events - Laboratory assessments.		
Methodology:	Phase IIIB , randomised, double-blind, placebo-controlled study with two parallel groups, fixed dose, multicentric national study		
Number of patients:	Planned: 550	Randomized: 174	Treated: 173
Evaluated:	ITT: 135 PP: 58	Safety: 173	
	The study was prematurely cancelled due to the decision of the sponsor to interrupt the clinical program of rimonabant		
Diagnosis and criteria for inclusion:	**Inclusion Criteria**: 1. Men or women aged ≥ 30 years and < 75 years. 2. Body mass index (BMI) > 27 kg/m2 and < 40 kg/m2. 3. Willingness and ability to comply with the study protocol. 4. Written informed consent at the time of enrolment into the study. 5. Waist circumference > 102 cm in men and > 88 cm in women. 6. Microalbuminuria ≥ 20 mg/g creatinine and < 300 mg/g creatinine in at least two of three morning urine samples taken on 3 separate days prior to the baseline visit. 7. Type 2 diabetes and/or dyslipidaemia. TYPE 2 DIABETES PATIENT DEFINITION FOR THIS STUDY: Patients with clinical diagnosis of DMT2 according to ADA criteria on treatment with diet + sulfonylurea or glinide and/or metformin and HbA1c < 9%. The antidiabetic treatment must be stable for a minimum of 4 weeks prior to the screening visit. DYSLIPIDAEMIA PATIENT DEFINITION FOR THIS STUDY:		

	Patient untreated or treated with statins and/or ezetimibe and/ or fibrates at stable doses for a minimum of 8 weeks before the screening visit, with LDL-C < 155 mg/dL (4.00 mmol/L) And meeting at least one of the following criteria: HDL-C < 40 mg/dL (1.03 mmol/L) for men and < 50 mg/dL (1.29 mmol/L) for women. Triglyceridaemia ≥ 150 mg/dL (1.69 mmol/L) and ≤ 400 mg/dL (4.52 mmol/L) **Exclusion Criteria**: 1. Breastfeeding or pregnant women or who expect to become pregnant. 2. Non-use of approved methods of contraception in women of child-bearing potential. 3. History of very low calorie diet in the 3 months prior to the screening visit (<1200 kcal/day). 4. Change in weight > 5 kg in the 3 months prior to the screening visit. 5. History of surgery for weight loss (such as vertical banded gastroplasty, gastric by-pass, etc.) 6. History of bulimia or anorexia nervosa according to DSM-IV definition. 7. Any clinically significant endocrine disorder, in the opinion of the investigator, especially known alterations in the blood concentration of thyroid-stimulating hormone and free thyroxine. Note: euthyroid patients subject to replacement treatment can be included if the dosage of thyroxin remains stable for a minimum of 3 months prior to the screening visit. 8. Type 1 Diabetes 9. Triglyceridaemia > 400 mg/dL (4.52 mmol/L) 10. Severe renal dysfunction (creatinine clearance < 30 mL/min) or glomerular filtration rate < 30 mL/min/1.73 m2 (MDRD 4 variables formula). 11. Chronic Hepatitis or clinically known significant liver disease or ALT and/or AST > 3x the upper limit of the normal range at the screening visit. 12. Systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at screening (before randomization). 13. Presence of any condition (medical, including clinically significant abnormal laboratory tests, physiological, social or geographical) actual or anticipated that the investigator feels would compromise the patient's safety or limit his/her successful participation to the study. Above all:

	• Cardiac abnormalities: cardiac failure status New York Heart Association III or IV, relevant acute abnormal finding seen on ECG at screening or within 6 months before screening, • Any current malignancy or any cancer within the past five years (except adequately treated basal cell skin cancer or cervix carcinoma in situ), • Significant haematology abnormalities (haemoglobin < 100 g/L and/or neutrophils < 1,500 cells/µL and/or platelets < 100,000 cells/µL), • Central nervous system disorders such as, for example, epilepsy, • Major depression or other psychiatric disorders, • Patients with a history of current suicidal ideation and/or with suicidal ideation and depressive disorder. 14. History of abuse of alcohol or other substances (except smoking). 15. Hypersensitivity or intolerance to the active ingredient or any of the excipients, such as lactose. Concomitant medication prior to the screening visit 16. Administration of any treatment undergoing clinical investigation (drug or medical device) in the 30 days prior to the screening visit 17. Previous treatment with rimonabant. 18. Administration of any of the following products in the 3 months prior to the screening visit • Anti-obesity drugs (such as, sibutramine or orlistat). • Other weight loss drugs (phentermine, anphetamines). • Weight loss herbal preparations. • Nicotinic acid, bile acid sequestrants or Omega 3 drugs (e.g. Omacor) • Prolonged use (more than a week) of systemic corticosteroids or neuroleptics • Antidepressants (including bupropion) • Insulin,(except an administration episode < 7 days) • thiazolidinediones, α-glucosidase inhibitors, or any combination of these antidiabetic drugs (except combination of sulfonylureas or glinides and metformin) 19. In type 2 diabetes patients, start of or change in treatment with sulfonylureas or glinides and/or metformin, in the 4 weeks prior to the screening visit. 20. Start of or change in treatment with antihypertensive drugs in the 12 weeks

	prior to the screening visit. 21. Start of or change in treatment with statins and/or ezetimibe and/or fibrates in the 8 weeks prior to the screening visit.
Investigational product: Dose: Administration: Batch number(s):	Rimonabant 20 mg/day Oral [redacted]
Duration of treatment: For each patient: 15 days screening + treatment for 12 months.	
Reference therapy: Dose: Administration: Batch number(s):	Placebo of Rimonabant 20 mg/day Oral [redacted]

Criteria for evaluation:	Primary endpoint: Relative change between the baseline situation and month 12 in terms of microalbuminuria levels. Secondary endpoints: Percentage of patients whose albuminuria levels decrease, stabilise, increase towards macroalbuminuria or remain unchanged between the baseline visit and month 12. Relative and absolute change between the baseline situation and month 12 in terms of Weight Waist circumference BMI Total cholesterol HDL cholesterol (HDL-C) LDL cholesterol (LDL-C) Triglycerides Apolipoprotein B Apolipoprotein A1 Fasting glycaemia Fasting insulinaemia HbA1c hs--CRP Cytokines (IL-6, TNF-α). Adipocytokines: adiponectin Glomerular filtration rate Blood pressure Quality of Life assessment (IWQOL questionnaire) Incidence of AEs in each group, including neuropsychiatric events Laboratory assessments
Statistical methods:	**Study population:** A patient was considered **evaluable for the safety analysis**, and therefore for the descriptive analysis, when he/she received at least one dose of study treatment, regardless of whether or not the patient met the inclusion/exclusion criteria or whether important efficacy-related information was unavailable.

	For the **efficacy analysis,** the values of **evaluable patients for intention to treat (ITT)** were used. The ITT sample consisted of randomised patients who received at least one dose of study medication administered under double-blind conditions, who met all the selection criteria for the study, and who presented the baseline evaluation of albuminuria / creatinine (mg/g) in urine (primary endpoint), and at least one evaluation subsequent to the baseline visit. Additionally, the efficacy analysis for the primary efficacy endpoint was also performed for the evaluable population **per-protocol (PP)**, defined as the ITT population in which no deviation from the protocol was reported in the baseline situation or during the course of the study. The PP sample consisted of randomised patients who received at least 80% of the doses of study medication administered under double-blind conditions, who met all the selection criteria for the study, and who presented the baseline evaluation and evaluation from all subsequent visits of albuminuria / creatinine (mg/g) in urine (primary endpoint). The continuous data were summarised for each treatment group using the number of observations available (N), the mean, the standard deviation, the minimum, the median and the maximum. The categorical data were summarised for each treatment group using counts and percentages. Unavailable data were not categorised in the summaries. In general terms, descriptive statistics were provided for the quantitative efficacy and safety endpoints (result and change in relation to the baseline situation) per visit for the cases observed, i.e. only patients for whom no evaluations were unavailable for each of the nominal visits. The continuous evaluation criteria were analysed using an analysis of covariance (ANCOVA) with the baseline situation as a covariable; this was specifically the case with the principal statistical comparison. The categorical data were analysed using Pearson's $\chi 2$ test. Fisher's exact test was used for low-density cells. All the statistical tests were bilateral. All the analyses were performed using SAS software version 9 or higher. The values that were unavailable were considered to be missing data, i.e. only the observed values were used in the data analyses and presentations. The only exception was in the ITT population for the principal analysis, where the concept of last observation carried forward was used. **Efficacy:** The primary endpoint is the relative change between the baseline situation and month 12 in terms of microalbuminuria levels (albumin/creatinine ratio [mg/g] in urine). A

	statistical test was used for independent samples (Student t-test or Mann-Whitney U test) to compare the percentage of relative change between the baseline situation and month 12 in terms of microalbuminuria levels in both treatment groups (Rimonabant and placebo). The primary endpoint was also analysed using an ANCOVA with the treatment (Rimonabant or placebo) as a fixed effect and with the baseline evaluation as a covariable. A bilateral type I error of 0.05 was used. The effect of the centre and the centre-treatment interaction was analysed with a random-effect model (mixed model). The secondary efficacy endpoints were summarised by treatment group with descriptive statistics. Body weight and waist circumference were analysed using an ANCOVA of repeated measurements with the treatment and the visit as fixed effects and the baseline evaluations as a covariable. The principal statistical comparison was performed in month 12 using the relevant comparison within the framework of the ANCOVA of repeated measurements. The dependent variable used for the models was the relative change in relation to the baseline situation. The other secondary endpoints with data on more than two visits were analysed in a similar manner. For the other secondary continuous variables with just two evaluations, one in the baseline situation and the other at the end of the trial, the same ANCOVA model was used as with the primary endpoint. The categorical efficacy endpoints were analysed using the $\chi 2$ test or, if that was not suitable, using Fisher's exact test, applied to month 12. **Safety:** The safety analysis was based on the AEs reported and other safety information. For the final analysis, the Sponsor applied its most up-to-date list of potentially clinically significant abnormalities (PCSA) to the results of the clinical analyses, vital signs and electrocardiograms (ECGs). The Pharmacovigilance Department of Sanofi-Aventis classified the AEs as "occurred during treatment" or "did not occur during treatment". Adverse events described in the screening and/or baseline visit before receiving the study treatment which lasted throughout the study were considered to be pre-existing, unless the severity of the symptoms increased after the first dose of treatment. The Sponsor coded all AEs recorded during the course of the study according to the MedDRA system and assigned them to an organ system. A Treatment Emergent Adverse Event (TEAE) is an AE that occurs or worsens during the study treatment or during the 5 half-lives following the last dose of the drug substance.

	Each time the same TEAE occurred subsequently, it was considered a "repeat". All TEAEs were analysed independently of their relationship with the treatment. The following information was provided for each treatment group. - Summary tables of the number and percentage of patients with at least one TEAE, number and percentage of each TEAE classified by organ system and in decreasing order of frequency by preferred term. - Maximum severity: the maximum severity was described bearing in mind possible repeats of each TEAE. The analysis focused on the values with PCSAs. The patients with PCSAs were identified in each analysis. The number and percentages of patients with PCSAs was summarised, at any interval subsequent to randomisation, for all the variables analysed for the purposes of vital signs. The summaries included patients who were exposed to the study medication in whom at least one determination of their vital signs had been performed following the first administration of the study medication. When the definition of the PCSA involved the change in relation to the baseline value, it was also necessary to have a baseline value for the patients to include in the summaries. In these descriptions, the baseline value was the last available value before the drug was taken. Descriptive statistics were also used to summarise the results and the changes in relation to the baseline situation in each treatment group. A list of marks indicating out-of-range values was also provided, as were the values with PCSAs. The following information was summarised for each treatment group. • Number and percentage of patients who suffered at least one serious AE. • Number and percentage for each preferred term, classified in decreasing order of frequency with each organ system, total number of serious AEs.

Summary:	**Efficacy results** The overall mean percentage of compliance with the treatment was 97% in the group treated with Rimonabant and 97.5% in the placebo group. In both groups it was equal to or more than 96% over the course of the different study visits. With regard to the primary objective of the study, evaluating the effect of Rimonabant compared to placebo on microalbuminuria levels over a 12-month period, it was observed that the patients treated with Rimonabant presented a reduction in microalbuminuria levels after 12 months in relation to the baseline levels, whereas in the patients who received placebo, the microalbuminuria levels after 12 months had increased in relation to the baseline levels. Therefore, the variable studied as the percentage change in levels showed a negative value in the patients in the experimental group and a positive value in the patients in the placebo group. The differences were statistically significant in the ITT population, where the percentage change was -13.6% in the Rimonabant group and 53.6% in the placebo group ($p<0.0001$). In the PP population, the same direction of change was found in both groups (Rimonabant: -6.9%; placebo: 29.9%) although the differences were not statistically significant. The percentage of relative change in microalbuminuria levels after 12 months in the ITT population was significant for the placebo group, as the results indicated that the levels increased, whereas for the Rimonabant group, although estimate of this parameter did indicate a decrease in macroalbuminuria levels, the decrease was not statistically significant. The results showed the same trend for the PP population, although statistical significance was not reached in either of the two groups. With regard to the secondary objectives considered, no statistically significant differences were observed between the two groups in terms of the evolution of microalbuminuria and the absolute change in these levels. Likewise, no differences were observed in the percentages of patients who presented a decrease, increase or stabilisation of microalbuminuria levels after 12 months of treatment with Rimonabant or placebo. It should be mentioned that 41.9% of the patients treated with Rimonabant and 40.7% of those who received placebo experienced a decrease in microalbuminuria levels after 12 months of treatment. The patients treated with Rimonabant showed a statistically higher reduction (absolute and relative change) in the different anthropometric variables analysed: weight, waist circumference and BMI. In terms of the lipid profile, the analysis of the change (absolute and relative) in the different parameters analysed showed statistically significant differences in total cholesterol, HDL-C and apolipoprotein A. The patients treated with Rimonabant showed an increase in total cholesterol values (absolute change: 8.1; relative change: 5.1), whereas the patients in the placebo group showed a reduction in these values (absolute change: -19.0; relative change: -8.1) ($p=0.0124$ and $p=0.0127$ respectively). In the case of HDL cholesterol, the change indicated an increase for the patients treated with Rimonabant (absolute change: 5.9; relative change: 13.6) and a reduction for the patients who received placebo (absolute change: -1.7; relative change: -3.0) ($p<0.0001$ for all the comparisons). And with regard to apolipoprotein A, the change again indicated an increase for the patients treated with Rimonabant (absolute

change: 13.3; relative change: 9.6) and a reduction for the patients who received placebo (absolute change: -6.1; relative change: -3.1) (p=0.0002 and p=0.0003 respectively).

No statistically significant differences between the two groups were observed in the change in the other parameters studied (LDL-C, triglycerides, apolipoprotein B).

No statistically significant differences were observed in the change (absolute and relative) in the glycaemia control parameters: fasting glycaemia and insulinaemia. For glycosylated haemoglobin, in the group treated with Rimonabant, the change indicated a reduction in HbA1c values (absolute change: -0.4; relative change: -4.6) and an increase in the patients in the placebo group (absolute change: 0.2; relative change: 2.3) (p=0.0083 and p=0.0124 respectively).

The analysis relating to adipocytokines and inflammatory markers showed significant differences between the two groups in the absolute and relative change in adiponectin values (Rimonabant: absolute change: -0.4; relative change: 8.6; Placebo: absolute change: -3.9; relative change: 26.2) (p=0.0017 and p=0.0004 respectively). In terms of inflammatory markers, statistically significant differences in the change (absolute and relative) were also observed between the two study groups. The patients treated with Rimonabant experienced a reduction in hs-CRP values (absolute change: -2.1; relative change: -17.3), whereas the patients who received placebo showed an increase in the values (absolute change: 1.5; relative change: 138,1) (p= 0,0327 y p= 0,0219 respectively).

Concerning IL-6, an increased was showed for both groups, higher in placebo group (Rimonabant: absolute change: 0,5; relative change: 62,8; Placebo: absolute change: 1,0; relative change: 139,8) (p= 0,0002 y p= 0,0003 respectively).

Finally, for both groups no differences were found in the change (absolute and relative) in glomerular filtration rate and in blood pressure values.

Safety results

The mean exposure time to the treatment was similar in both groups: 251.2 days for the experimental group and 262.0 for the placebo group.

Overall, 89.4% and 85.2% of the patients randomised in the Rimonabant group and placebo group, respectively, presented an AE.

A total of 180 events were reported: 148 non-neuropsychiatric AEs and 32 neuropsychiatric AEs.

The distribution by groups was as follows:

In the Rimonabant group: 93 non-neuropsychiatric AEs reported in 46 patients and 29 neuropsychiatric AEs reported in 20 patients. Of these, 35 non-neuropsychiatric AEs in 21 patients were considered by the investigator to be related to the study medication and 14 neuropsychiatric AEs in 9 patients were considered by the investigator to be related to the study medication.

In the placebo group: 55 non-neuropsychiatric AEs reported in 35 patients and 3

	neuropsychiatric AEs reported in 3 patients. Of these, 5 non-neuropsychiatric AEs in 3 patients were considered by the investigator to be related to the study medication. None of the neuropsychiatric AEs in the placebo group were considered to be related to the study medication. To summarise, for the patients treated with Rimonabant, a total of 122 AEs were reported, of which 49 (40.2%) were considered to be related to the drug, and in the placebo group 58 AEs were reported, 5 (8.6%) of which were considered to be related to the treatment. The most common non-neuropsychiatric AEs in the group treated with Rimonabant were gastrointestinal disorders (26.9%), especially nausea (40% of the gastrointestinal AEs), followed by infections and infestations (20.4%). The majority of neuropsychiatric AEs were psychiatric disorders (55.2%; 16 out of a total of 29), especially anxiety (25% of the psychiatric disorders). In the placebo group, the most common non-neuropsychiatric AEs were infections and infestations (19%) followed by musculoskeletal and connective tissue disorders (16.4%). The majority of neuropsychiatric AEs were nervous system disorders (66.7%; 2 out of a total of 3). 12 serious AEs were reported, 7 (58,3 %) in the Rimonabant group and 5 (41,7 %) in the placebo group. Serious AEs for the group treated with Rimonabant were: cutaneous lupus erythematosus, postoperative wound infection, rhabdomyolysis, acute hepatitis, ischaemic cardiomyopathy, chronic obstructive pulmonary disease and intermittent claudication. Serious AEs reported in the placebo group were: coronary syndrome, rectal haemorrhage, chest pain, angina pectoris, carcinoma papillary of thyroid. One accidental overdose was reported for a patient in the placebo group, which was asymptomatic. The percentages of patients with potentially clinical significant alterations (PCSA) in the analytical parameters and vital signs post-treatment were similar in both groups. At baseline, the percentage of patients in Rimonabant group with PCSA was lower than in the placebo group for glucose and Hb1Ac, whereas in the average of microalbuminuria, MCH and hs-CPR, the percentage of patients in Rimonabant group with PCSA was higher. In the postreatment, lower percentages of patients with PCSA in the Rimonabant group were observed compared with placebo group in the following parameters: HDL-C, Hb1Ac (for which basal differences were already observed), adiponectin and insulin resistance. No differences in sociodemographic variables were observed between the patients who received Rimonabant and those who received placebo in terms of the occurrence of neuropsychiatric AEs. It is important to mention that, even no statistically significant differences were observed, the percentage of patients with neuropsychiatric AEs and neurological and psychiatric records reported in previous medical relevant history was higher in Rimonabant group compared with the placebo group. Differences were not observed intra groups, in each of the groups according to the presence or absence of neuropsychiatric AEs.

Conclusions:	[redacted]
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