SYNOPSIS

Title of the study:	A randomized, double blind, two arm, parallel, placebo controlled study of rimonabant 20mg effect on high density lipoprotein kinetics in patients with abdominal obesity and additional cardio metabolic risk factors.
Investigator:	No principal investigator
Study centers:	The study was conducted in 5 centers in 4 countries (France, Finland, UK, Australia)
Publications (reference): None	
Study period:	
Date first patient enrolled:	31 October 2006
Date last patient completed:	18 December 2008
Phase of development:	Phase 3b/4 (phase 3b in Australia and phase 4 in Europe)
Objectives:	
The objectives of the protocol were as follows:	
Primary: - To assess the effect of rimonabant on HDL ApoA-I fractional catabolic rate (FCR).	
Secondary: To assess the effect of rimonabant on HDL ApoA-I production rate (PR) and on other lipoprotein kinetics.	
To assess the effect of rimonabant on lipids, glycemic and inflammatory parameters.	
To assess the effect of rimonabant on body composition.	
To assess the safety of 12 months rimonabant treatment versus placebo.	
The study was stopped prematurely after 64 patients had been randomized, due to the Sponsor's decision to discontinue the rimonabant clinical program. Consequently, the analysis (as defined in the statistical analysis plan) focused on a review of the safety profile based on reporting of adverse events (AEs). The data which are presented in this synopsis report are also supported by limited appendices.	
Methodology: This was a phase 3b/4, multicenter, randomized using minimization, double-blind, placebo-controlled two-arm parallel study	
Number of patients:	Planned: 80 patients Randomized: 64 patients Screened: 310 patients Treated: 63 patients Run-in: 118 patients
Evaluated:	Safety: 63 patients
Diagnosis and criteria for inclusion: Abdominally obese patients aged 35-65 years of age with either fasting triglycerides between 1.7 mmol/L and 4.5 mmol/L or HDL <1.03 mmol/L in men and <1.29 mmol/L in women.	

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

Duration of treatment: 12 months

Duration of observation: 16.5 months

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

Criteria for evaluation:

Efficacy: Not applicable

Safety: Only AEs were reviewed and described in this synopsis.

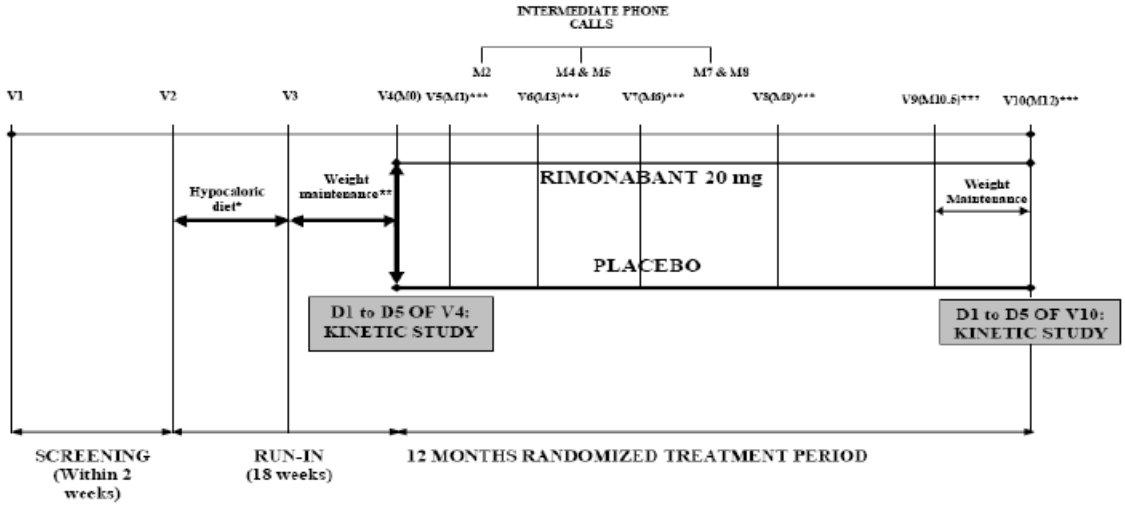
Statistical methods:

Efficacy: Not applicable

Safety: Safety analyses were carried out on the All Treated Population. Treatment Emergent Adverse Events (TEAEs) were summarized by treatment group using descriptive statistics.

Summary:

A summary of the study design is provided below, and a study flow-chart is provided at the end of the document.



* During this period, patients visited the dietician at V2+1 week, V2+3 weeks, V2+ 6 weeks and V2+ 9 weeks
** During this period, patients visited the dietician 3 weeks after starting the isocaloric diet
*** V5: 30±5 days after treatment start, V6: 60±5 days after V5, V7: 90±10 days after V5, V8: 90±10 days after V7, V9: 45±10 days after V8.

The study was divided into 3 phases:

- First, a screening phase (2 weeks) ;

- Second, a run-in phase composed of a 3-month drug-free run-hypocaloric diet phase followed by a 6-week drug-free weight maintenance phase ;

- And third, a 12-month double blind treatment randomization phase beginning with a 5-day kinetic study phase and ending with a 5-day kinetic study phase preceded by a 6-week weight maintenance phase

Summary of populations:

Populations	Placebo N=32		Rimonabant 20 mg N=32	
ITT Population	31	(96.9%)	31	(96.9%)
All Treated Population	31	(96.9%)	32	(100%)

Note: % calculated using the number of randomized patients as the denominator

One Patient in the rimonabant 20 mg group was excluded from the ITT population due to study discontinuation after receiving 4 days of treatment.

One Patient in the placebo group withdrew after randomization but before receiving any treatment.

Patient disposition:

42 randomized and treated patients were withdrawn from the study for reasons reported in the following table:

Withdrawals during the treatment period (All Treated Population)	Placebo N=31		Rimonabant 20 mg N=32	
Randomized and exposed	31	(100%)	32	(100%)
Completed study treatment period	11	(35.5%)	10	(31.3%)
Discontinued study treatment period	20	(64.5%)	22	(68.8%)
Reason for treatment discontinuation				
Adverse event	0	(0.0%)	4	(12.5%)
Subject's request	1	(3.2%)	0	(0.0%)
Other reason: sponsor's request	19	(61.3%)	18	(56.3%)

Note: % calculated using the number of patients from All treated population as the denominator
Note: sponsor's request refers to sponsor's decision to discontinue rimonabant clinical program

Most of the patients were withdrawn due to sponsor's request (discontinuation of Rimonabant development). All the patients withdrawn due to AEs were in the Rimonabant group (12, 5%).

Exposure:

Extent of exposure and treatment compliance were assessed in the All Treated Population as follows:

Extent of exposure (All Treated Population)	Placebo N=31	Rimonabant 20 mg N=32
Duration of exposure (days)		
n	30	32
Mean (SD)	237.4 (118.7)	209.6 (125.4)
Median	276.0	222.0
Min/Max	15 / 372	4 / 365
Treatment duration n (%)		
1-60 days	3 (9.7%)	5 (15.6%)
61-90 days	1 (3.2%)	3 (9.4%)
91-180 days	7 (22.6%)	6 (18.8%)
181-270 days	4 (12.9%)	5 (15.6%)
271-315 days	3 (9.7%)	2 (6.3%)
316-360 days	10 (32.3%)	10 (31.3%)
>360 days	2 (6.5%)	1 (3.1%)

Note: Number corresponds to the count of patients with non missing data

The mean duration of exposure was slightly longer in the placebo group (237.4 days) than in the rimonabant 20 mg group (209.6 days). The distribution of patient treatment durations was similar between the two treatment groups.

Demographics:

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

Demographics Randomized population	Placebo N=32	Rimonabant 20 mg N=32	Total N=64
Age* (years)			
n	32	32	64
Mean (SD)	50.6 (8.7)	52.8 (7.4)	51.7 (8.1)
Median	50.2	53.3	52.1
Min/Max	38 / 64	39 / 64	38 / 64
Gender, n (%)			
n	32	32	64
Male	27 (84.4%)	23 (71.9%)	50 (78.1%)
Female	5 (15.6%)	9 (28.1%)	14 (21.9%)
Race, n (%)			
n	32	32	64
Caucasian	32 (100%)	32 (100%)	64 (100%)
Waist circumference (cm)			
n	32	32	64
Mean (SD)	108.03 (6.99)	108.44 (8.67)	108.23 (7.82)
Median	109.00	108.33	108.58
Min/Max	95.7 / 120.3	87.3 / 124.0	87.3 / 124.0
Height (cm)			
n	32	32	64
Mean (SD)	177.2 (8.4)	173.4 (10.5)	175.3 (9.6)
Median	177	175	175
Min/Max	161 / 189	153 / 197	153 / 197
Weight (kg)			
n	32	32	64
Mean (SD)	99.94 (13.01)	97.07 (14.38)	98.50 (13.68)
Median	97.05	95.80	96.25
Min/Max	80.6 / 134.7	74.8 / 134.7	74.8 / 134.7
BMI* (kg/m^2)			
n	32	32	64
Mean (SD)	31.83 (3.30)	32.26 (3.54)	32.05 (3.40)
Median	31.81	31.51	31.81
Min/Max	24.8 / 37.8	25.8 / 38.3	24.8 / 38.3

Note: % calculated using the number of randomized patients as the denominator

All demographic and baseline characteristics were similar in both treatment groups. The majority of patients were male (78.1%) and all were Caucasian. The mean patient age was 51.7 ± 8.1 years. The mean waist circumference was 108.23 ± 7.82 cm. The mean BMI was 32.05 ± 3.4 kg/m^2 with a range of 24.8 kg/m^2 to 38.3 kg/m^2.

Efficacy results: Not applicable.

Safety results:

- Overview of AEs

Overall incidence of TEAEs is summarized and displayed in the following table for the All Treated Population:

TEAE Category **All Treated Population**	**Placebo** **N=31**	**Rimonabant 20 mg** **N=32**	**p-values**
Patients with any TEAEs (including SAEs)	23 (74.2%)	24 (75.0%)	1.0000
Patients with any serious TEAEs (including SAEs leading to death)	0 (0.0%)	1 (3.1%)	1.0000
Patients with any TEAEs leading to death	0 (0.0%)	0 (0.0%)	NA
Patients permanently discontinuing treatment due to TEAEs	0 (0.0%)	4 (12.5%)	0.1132

n (%) = number and percentage of patients with at least one adverse event
TEAEs: treatment emergent adverse events, refers to AEs with date of onset/worsening/seriousness during study drug exposure up to 75 days following the last study drug intake p-values refer to Fisher's exact test

The number of patients who experienced TEAEs was similar in both groups: 23 (74.2%) in the placebo group and 24 (75.0%) in the rimonabant 20 mg group. Serious TEAEs and TEAEs leading to study drug discontinuation were observed in the rimonabant group, 1 (3.1%) and 4 (12,5%) respectively. No deaths occurred during the study.

- Summary of TEAEs

All TEAEs are summarized by preferred term (PT) (in order of descending frequency by body system in the rimonabant 20 mg group, cut-off: PT≥ 5% in either treatment group) in the following table:

TEAEs by body system and by PT All Treated Population	Placebo N=31		Rimonabant 20 mg N=32	
Anxiety	2	(6.5%)	9	(28.1%)
Diarrhoea	2	(6.5%)	8	(25.0%)
Insomnia	1	(3.2%)	7	(21.9%)
Dizziness	2	(6.5%)	5	(15.6%)
Headache	0	(0.0%)	5	(15.6%)
Hot flush	0	(0.0%)	4	(12.5%)
Nausea	0	(0.0%)	4	(12.5%)
Nasopharyngitis	5	(16.1%)	3	(9.4%)
Stress	4	(12.9%)	3	(9.4%)
Fatigue	2	(6.5%)	3	(9.4%)
Depressed mood	1	(3.2%)	3	(9.4%)
Paraesthesia	1	(3.2%)	3	(9.4%)
Tearfulness	1	(3.2%)	3	(9.4%)
Back pain	0	(0.0%)	3	(9.4%)
Muscle spasms	0	(0.0%)	3	(9.4%)
Pharyngolaryngeal pain	0	(0.0%)	3	(9.4%)
Decreased appetite	3	(9.7%)	2	(6.3%)
Arthralgia	2	(6.5%)	2	(6.3%)
Constipation	2	(6.5%)	2	(6.3%)
Hypoaesthesia	2	(6.5%)	2	(6.3%)
Abdominal pain	1	(3.2%)	2	(6.3%)
Early morning awakening	1	(3.2%)	2	(6.3%)
Abdominal pain upper	0	(0.0%)	2	(6.3%)
Abnormal dreams	0	(0.0%)	2	(6.3%)
Confusional state	0	(0.0%)	2	(6.3%)
Disturbance in attention	0	(0.0%)	2	(6.3%)
Dysphagia	0	(0.0%)	2	(6.3%)
Heart rate increased	0	(0.0%)	2	(6.3%)
Malaise	0	(0.0%)	2	(6.3%)
Micturition urgency	0	(0.0%)	2	(6.3%)
Pain in extremity	0	(0.0%)	2	(6.3%)
Toothache	0	(0.0%)	2	(6.3%)
Tremor	0	(0.0%)	2	(6.3%)
Anger	2	(6.5%)	1	(3.1%)
Blood pressure increased	2	(6.5%)	1	(3.1%)
Cough	2	(6.5%)	1	(3.1%)
Influenza	2	(6.5%)	1	(3.1%)
Sinusitis	2	(6.5%)	1	(3.1%)
Vomiting	2	(6.5%)	1	(3.1%)
Musculoskeletal pain	3	(9.7%)	0	(0.0%)
Accidental overdose	2	(6.5%)	0	(0.0%)
Faeces hard	2	(6.5%)	0	(0.0%)
Tonsillitis	2	(6.5%)	0	(0.0%)

n (%) = number and percentage of patients with at least one adverse event
TEAEs: treatment emergent adverse events, refers to AEs with date of onset/worsening/seriousness during study drug exposure up to 75 days following the last study drug intake
Note: PT sorted by decreasing frequency order in Rimonabant 20 mg group then in placebo group. In case of equal frequency regarding PT, alphabetical order is used.
AEs coded using MedDRA 10.0

The most frequent TEAEs reported by PT were : anxiety (6.5% in the placebo group versus 28.1% in the rimonabant 20 mg group), diarrhea (6.5% versus 25.0%, respectively) insomnia (3.2% versus 21.9%, respectively), dizziness (6.5% versus 15.6%, respectively), headache (0.0% versus 15.6%, respectively), hot flush (0.0% versus 12.5%, respectively), nausea (0.0% versus 12.5%, respectively), nasopharyngitis (16.1% versus 9.4%) and stress (12.9% versus 9.4%).

Except for nasopharyngitis and stress, those TEAEs were more frequently seen in patients receiving rimonabant 20 mg than in those receiving placebo.

All other TEAE incidences by PT were comparable in both treatment groups.

In terms of TEAEs reported by SOC, infections and infestations were the most frequently observed in the placebo group (38.7%), while psychiatry disorders and gastrointestinal disorders (40.6% in each) were the most commonly reported in the rimonabant 20 mg group.

Gastrointestinal disorders (22.6% in the placebo group versus 40.6% in the rimonabant 20 mg group), nervous system disorders (19.4% versus 34.4%, respectively), general disorders and administration site conditions (9.7% versus 21.9%, respectively), and vascular disorders (3.2% versus 15.6%, respectively) were more frequently seen in patients receiving rimonabant 20 mg than in those receiving placebo. Infections and infestations (38.7% in the placebo group versus 25.0% in the rimonabant 20 mg group) were more frequently seen in patients receiving placebo than in those receiving rimonabant 20 mg.

- Summary of SAEs

In the All Treated Population, 1 serious TEAE (gastroenteritis) was reported in one patient in the rimonabant 20 mg group.

Three further post-treatment emergent SAEs (adenoma benign, myoclonus, prostate cancer) were reported in one patient in the rimonabant 20 mg group.

Two SAEs occurred in 2 patients during the initial run in (erysipelas in one patient and breast cancer in one patient). These two patients were not randomized to treatment.

The SAEs for 2 patients are detailed in the narrative section of the CSR.

- Summary of Deaths

No patients died during this study.

Conclusions: [redacted]

Date of report: 11 June 2009