SYNOPSIS

Title of the study:	A randomized, double-blind, parallel-group, multicenter, multinational study to assess the long-term effect, over 1 year, of rimonabant 10 mg in comparison with rimonabant 20 mg after an initial treatment period of 6 months with rimonabant 20 mg in overweight or obese patients (EFC10139)
Investigators:	No Principal Investigator was planned or identified for this study
Study centers:	The study was conducted at 31 centers in 5 countries (Croatia, Finland, Hungary, the Netherlands, and Romania).
Publications (reference):	None
Study period:	
Date first patient enrolled:	22 April 2008
Date last patient completed:	26 February 2009
Phase of development:	Phase 3b

Objectives: The objectives of the protocol were as follows:

Primary: To assess, over a period of 12 months (1 year), the effect on weight loss and weight maintenance of rimonabant 10 mg in comparison with rimonabant 20 mg in overweight/obese patients after an initial treatment period of 6 months with rimonabant 20 mg.

Secondary:

- To assess the effect of rimonabant over a period of 12 months (1 year) on: waist circumference, high-density lipoprotein cholesterol and triglycerides, fasting plasma glucose, fasting insulin.
- To evaluate the long-term safety and tolerability of rimonabant 10 mg and 20 mg over a period of 12 months followed by a 75-day posttreatment follow-up period (1 year + 75 days), after randomization, in overweight/obese patients.

The study was stopped prematurely after 332 patients entered the run-in period, of whom only 3 patients had been randomized, due to the Sponsor's decision to discontinue the rimonabant development program. The monitoring therefore focused on a review of the safety profile, based on the reporting of adverse events. Given that only 3 patients were randomized for a maximum duration of 11 days, the primary analysis on weight change was not performed. As a result, the analysis (as defined in the statistical analysis plan) focused on the run-in rimonabant 20 mg treatment period and the results are presented through a synopsis-style report. Appendices attached to this synopsis-style report were chosen to provide the relevant information.

Methodology: This was a multicenter, randomized, double-blind, 2-arm parallel group study, intending to compare rimonabant 10 mg with rimonabant 20 mg, following a 6-month open-label run-in rimonabant 20 mg treatment period.

Number of patients:	Planned: 522 (run-in); 444 (randomized)	Run-in: 332	Randomized: 3	Treated: 331
Evaluated:	Run-in exposed : 331			

Diagnosis and criteria for inclusion: Male or female patients aged ≥18 years, with a body mass index (BMI) ≥30 kg/m², or BMI >27 kg/m² with associated risk factor(s) such as type 2 diabetes or dyslipidemia.

Investigational product: Rimonabant 10 mg tablet

Dose: 10 mg tablet once daily

Administration: Oral (before breakfast)

Batch number: [redacted]

Duration of treatment: Run-in period: 6 months; double-blind period: 12 months

Duration of observation: Approximately 21.5 months (including a 1- to 2-week screening period, 6-month open-label run-in period, 12-month double-blind treatment period, and 75-day posttreatment follow-up)

Reference therapy: Rimonabant 20 mg tablet

Dose: 20 mg tablet once daily

Administration: Oral (before breakfast)

Batch number: [redacted]

Criteria for evaluation:

Efficacy: No analyses were performed on the primary efficacy variable (absolute change in body weight from baseline [randomization] to Month 12) as only 3 patients were randomized. Only the evolution of body weight (absolute value and change from the entry in the run-in period) was described over the run-in period with rimonabant 20 mg.

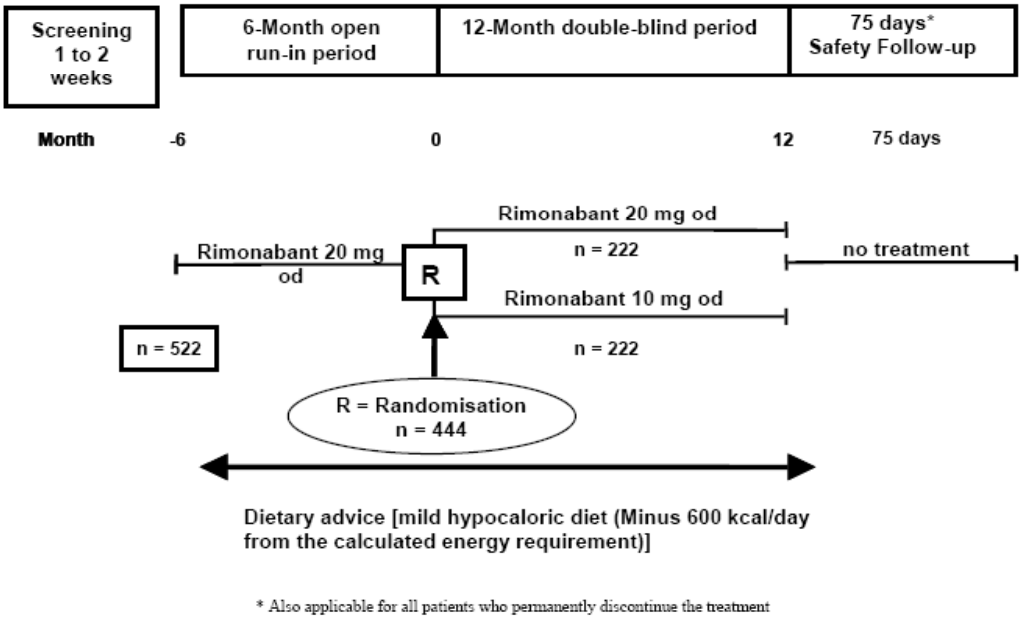
Safety: Only adverse events were reviewed and described.

Statistical methods:

Efficacy: The evolution of body weight (absolute value and change from the entry in run-in period) was described by visit over the run-in period in the run-in population. The run-in population consists of patients who received an open run-in batch number at Visit 2 (based on enrollment process and recorded in the interactive voice randomization system [IVRS] database). Data included in this analysis up to Visit 7 (5 months of run-in) correspond to the evaluated patients at each visit. At Visit 8, data corresponded to either the evaluation at the discontinuation visit for run-in failure or at the randomization visit for the randomized patients.

Safety: Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1 and summarized, using descriptive statistics, in the run-in and exposed population, which corresponds to patients exposed to the study medication (open run-in treatment or double-blind treatment), regardless of the amount of treatment administered.

Summary: A summary of the study design is provided below, and a study flow-chart (per protocol amendment) is provided in Figure 1 after the synopsis.



Summary of populations: Due to the low number of patients randomized in this study, only the run-in population is presented.

Patient disposition: A total of 332 patients entered the run-in period, of them 331 received rimonabant 20 mg. None of the patients completed the study as planned. Most patients discontinued treatment as a result of the premature stop of the study and were counted in the category "other reason". Table 1 summarizes patient disposition including reasons for run-in discontinuation. Only 3 patients were randomized after the run-in period, all in the rimonabant 10 mg group, and discontinued as a result of the premature stop of the study.

Table 1 - Summary of patients disposition – end-of-treatment – n (%) – screened patients

	Screened patients (N=398)
Screened failure patients	66 (16.6%)
Reason for screen failure	
Inclusion/Exclusion criteria not respected	25 (6.3%)
Adverse event	0
Subject's request	5 (1.3%)
Poor compliance to protocol	0
Lost to follow-up	0
Other reason	36 (9.0%)
Run-in patients	332 (83.4%)
Run-in and exposed patients	331 (83.2%)
Discontinued the open run-in period	
Reason for discontinuation	
Adverse event	33 (8.3%)
Inclusion/Exclusion criteria not respected	3 (0.8%)
Subject's request	7 (1.8%)
Poor compliance to protocol	0
Lost to follow-up	0
Other reason	286 (71.9%)
Non Randomized and treated with double-blind treatment	0
Randomized patients	3 (0.8%)

Exposure: The run-in and exposed population included 331 patients exposed to at least 1 dose of rimonabant. Table 2 presents the global duration of study treatment regardless of the period (only run-in period for run-in patients and run-in plus double-blind periods for the randomized patients). The 3 randomized patients were exposed to rimonabant 10 mg during 3, 10, and 11 days, respectively. Given the short exposure to 10 mg and the long half-life of rimonabant (15 days), this dose was not assessed separately. The 3 randomized patients in the rimonabant 10 mg arm were analyzed as part of a unique rimonabant arm including all patients having received essentially 20 mg throughout the trial.

Table 2 – Summary of exposure to rimonabant - run-in and exposed population

	Rimonabant 20mg (N=331)
Cumulative exposure (patient years)	68.0
Extent of exposure (days)	
Number	331
Mean (SD)	75.0 (57.1)
Median	49.0
Min : Max	1 : 193
Count of patients [n(%)]	
1 - 30 days	101 (30.5%)
31 - 60 days	78 (23.6%)
61 - 90 days	25 (7.6%)
91 - 120 days	28 (8.5%)
121 - 150 days	44 (13.3%)
151 - 180 days	50 (15.1%)
≥ 181 days	5 (1.5%)

Note: Only run-in period for run-in patients and run-in and double-blind periods for randomized patients

Demographics: Patient demographic characteristics are presented in Table 3.

Table 3 - Summary of patient demographics at baseline - run-in population

	Rimonabant 20mg (N=332)
Age (years)	
Number	332
Mean (SD)	51.8 (13.2)
Median	54.0
Min : Max	18 : 78
[18-44]	104 (31.3%)
[45-64]	169 (50.9%)
≥ 65	59 (17.8%)
Gender, n(%)	
Number	332
Male	128 (38.6%)
Female	204 (61.4%)
Race, n(%)	
Number	332
Caucasian/White	324 (97.6%)
Black	0
Asian/Oriental	4 (1.2%)
Other	4 (1.2%)
Waist circumference (cm)	
Number	331
Mean (SD)	116.1 (13.8)
Median	114.7
Min : Max	84 : 170
For men, n(%)	
≤ 102 cm	8 (2.4%)
> 102 cm	119 (35.8%)
For women, n(%)	
≤ 88 cm	4 (1.2%)
> 88 cm	200 (60.2%)
Height (cm)	
Number	331
Mean (SD)	169.1 (9.9)
Median	168.0
Min : Max	141 : 198
Weight (kg)	
Number	331
Mean (SD)	105.9 (21.2)
Median	102.4
Min : Max	69 : 228
BMI (kg/m^2)	
Number	331
Mean (SD)	36.9 (5.8)
Median	35.9
Min : Max	27 : 60
< 27	0
[27-30[	18 (5.4%)
[30-35[	120 (36.1%)
[35-40[	113 (34.0%)
≥ 40	80 (24.1%)

Efficacy results: Weight constantly decreased from baseline over time, with a mean weight loss of 7.16 kg in patients who completed the fifth month of treatment. At the last visit of the run-in period (ie, Visit 8, which corresponds to the end-of-treatment visit regardless of the time of investigational product discontinuation), a mean weight loss of 4.31 kg was observed. Results are provided in the CSR Appendix.

Safety results:

- **Overview of adverse events**

The incidences of patients with at least 1 treatment-emergent adverse event (TEAE) during the run-in period are presented in Table 4. There was 1 death.

Table 4 - Overview of TEAEs - run-in and exposed population

	Rimonabant 20mg (N=331)
Patients with any TEAE	174 (52.6%)
Patients with any serious TEAE	12 (3.6%)
Patients with any TEAE leading to death	1 (0.3%)
Patients with TEAE leading to permanent treatment discontinuation	32 (9.7%)

Notes: TEAE: Treatment Emergent Adverse Event
TEAE includes all AEs with an onset date during treatment period and up to 75 days following the last study drug intake

- **Summary of treatment-emergent adverse events**

Treatment-emergent adverse events reported in at least 5% of run-in and exposed patients are presented in Table 5. All TEAEs are presented by system organ class (SOC), high level group term (HLGT), high level term (HLT), and preferred term (PT) in the CSR Appendix.

Table 5 - Number (%) of patients experiencing at least 1 TEAE (cut-off: incidence ≥ 5%) by SOC and PT - run-in and exposed population

Primary System Organ Class Preferred term	Rimonabant 20mg (N=331)
Any Class	174 (52.6%)
Infections and infestations	68 (20.5%)
Nasopharyngitis	27 (8.2%)
Gastrointestinal disorders	66 (19.9%)
Nausea	35 (10.6%)
Diarrhoea	20 (6.0%)
Nervous system disorders	63 (19.0%)
Dizziness	24 (7.3%)
Headache	22 (6.6%)
General disorders and administration site conditions	41 (12.4%)
Irritability	19 (5.7%)

Notes: TEAE: Treatment Emergent Adverse Event
TEAE includes all AEs with an onset date during treatment period and up to 75 days following the last study drug intake
n(%) = number and percentage of patients with at least one treatment emergent adverse event. MedDRA version 11.1
Table sorted by decreasing incidence of Primary SOC and PT within SOC. In case of equal frequency regarding SOC, alphabetical order is used.

- **Summary of serious adverse events**

Twelve of 331 run-in and exposed patients experienced serious TEAEs during this study (Table 6). Two patients experienced suicidal ideation on treatment, which were reported by convention as serious adverse events. No suicidal behavior was reported. Please refer to the CSR Appendix for details presented as narratives.

Results of the Columbia Suicide-Severity Rating Scale (C-SSRS) are presented in the CSR Appendix and case report form pages for patients with a positive C-SSRS are provided in the CSR Appendix.

Table 6 - Number (%) of patients experiencing at least 1 serious TEAE by SOC and PT - run-in and exposed population

Primary System Organ Class Preferred term	Rimonabant 20mg (N=331)
Any Class	12 (3.6%)
Infections and infestations	1 (0.3%)
Pneumonia	1 (0.3%)
Gastrointestinal disorders	1 (0.3%)
Dyspepsia	1 (0.3%)
Nervous system disorders	3 (0.9%)
Tremor	1 (0.3%)
Epilepsy	1 (0.3%)
Transient ischaemic attack	1 (0.3%)
Psychiatric disorders	3 (0.9%)
Aggression	1 (0.3%)
Suicidal ideation	2 (0.6%)
Hypomania	1 (0.3%)
Major depression	1 (0.3%)
Injury, poisoning and procedural complications	2 (0.6%)
Road traffic accident	1 (0.3%)
Carbon monoxide poisoning	1 (0.3%)
Lower limb fracture	1 (0.3%)
Metabolism and nutrition disorders	1 (0.3%)
Diabetes mellitus	1 (0.3%)
Cardiac disorders	1 (0.3%)
Myocardial ischaemia	1 (0.3%)
Hepatobiliary disorders	1 (0.3%)
Cholecystitis acute	1 (0.3%)

Notes: TEAE: Treatment Emergent Adverse Event
TEAE includes all AEs with an onset date during treatment period and up to 75 days following the last study drug intake
n(%) = number and percentage of patients with at least one treatment emergent adverse event. MedDRA version 11.1
Table sorted by decreasing incidence of Primary SOC and PT within SOC for all TEAEs. In case of equal frequency regarding SOC, alphabetical order is used.

- **Summary of deaths**

One patient died following accidental carbon monoxide poisoning about 10 weeks after discontinuation of the investigational product. Details are presented in a narrative in the CSR Appendix.

- **Summary of treatment-emergent adverse events leading to treatment discontinuation**

Discontinuation of treatment due to TEAEs occurred in 32 patients (9.7%) of the run-in and exposed population. Table 7 summarizes these events by SOC and PT.

Table 7 - Number (%) of patients experiencing at least 1 TEAE leading to permanent treatment discontinuation by SOC and PT - run-in and exposed population

Primary System Organ Class Preferred term	Rimonabant 20mg (N=331)
Any Class	32 (9.7%)
Gastrointestinal disorders	7 (2.1%)
Nausea	1 (0.3%)
Diarrhoea	3 (0.9%)
Vomiting	3 (0.9%)
Dyspepsia	2 (0.6%)
Nervous system disorders	12 (3.6%)
Dizziness	5 (1.5%)
Memory impairment	3 (0.9%)
Disturbance in attention	2 (0.6%)
Hypoaesthesia	3 (0.9%)
Aphasia	2 (0.6%)
Dyskinesia	1 (0.3%)
Tremor	2 (0.6%)
Epilepsy	1 (0.3%)
Poor quality sleep	1 (0.3%)
Syncope	1 (0.3%)
Psychiatric disorders	21 (6.3%)
Depressed mood	8 (2.4%)
Insomnia	5 (1.5%)
Anxiety	1 (0.3%)
Decreased interest	3 (0.9%)
Aggression	4 (1.2%)
Nightmare	3 (0.9%)
Stress	2 (0.6%)
Agitation	1 (0.3%)
Tension	1 (0.3%)
Panic attack	1 (0.3%)
Suicidal ideation	1 (0.3%)
Burnout syndrome	1 (0.3%)
Mental status changes	1 (0.3%)
Nervousness	1 (0.3%)
Restlessness	1 (0.3%)
Sleep disorder	1 (0.3%)
Violence-related symptom	1 (0.3%)
General disorders and administration site conditions	11 (3.3%)
Irritability	6 (1.8%)
Fatigue	4 (1.2%)
Asthenia	2 (0.6%)
Musculoskeletal and connective tissue disorders	2 (0.6%)
Muscle twitching	2 (0.6%)
Skin and subcutaneous tissue disorders	1 (0.3%)
Hypoaesthesia facial	1 (0.3%)
Vascular disorders	1 (0.3%)
Flushing	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)
Cough	1 (0.3%)

Notes: TEAE: Treatment Emergent Adverse Event
TEAE includes all AEs with an onset date during treatment period and up to 75 days following the last study drug intake
n(%) = number and percentage of patients with at least one treatment emergent adverse event. MedDRA version 11.1
Table sorted by decreasing incidence of Primary SOC and PT within SOC for all TEAEs. In case of equal frequency regarding SOC, alphabetical order is used.

Conclusions: [redacted]
Date of report: 19-May-2009