SYNOPSIS

Title of the study: A double-blind, randomized, placebo-controlled, parallel group study of rimonabant 20 mg daily for the treatment of non-diabetic patients with nonalcoholic steatohepatitis (NASH) (EFC10143)
Investigators: No Principal Investigator was planned or identified for this study
Study centers: The study was conducted at 46 centers in 13 countries (Argentina, Australia, Belgium, Italy, Malaysia, Mexico, Poland, Puerto Rico, Romania, Spain, Switzerland, the Untied Kingdom, and the United States of America).
Publications (reference): None
Study period: Date first patient enrolled: 17 January 2008 Date last patient completed: 27 February 2009
Phase of development: Phase 3b
Objectives: This study was designed to evaluate the efficacy and safety of rimonabant in the treatment of NASH in non-diabetic patients. The objectives of the protocol were as follows: ***Primary:*** To demonstrate, in patients without comorbid diabetes following a minimum of 24 months treatment, the superiority of rimonabant 20 mg once daily over placebo for improving the severity of NASH as measured by histological features of liver injury. ***Secondary:*** To demonstrate, in patients without comorbid diabetes following a minimum of 24 months treatment, the superiority of rimonabant 20 mg once daily over placebo: • in severity of hepatic fibrosis as measured by hepatic fibrosis stage; • in level of circulating plasma adiponectin; • in level of circulating hyaluronate; • in degree of insulin sensitivity; and • in aspartate amino transferase (AST)/alanine amino transferase (ALT) level. The study was stopped prematurely after 165 patients had been randomized, due to the Sponsor's decision to discontinue the rimonabant development program. The monitoring therefore focused on the safety profile based on the reporting of adverse events. Given that the liver biopsy is an invasive procedure, Investigators were not requested to perform the biopsy at the end-of-treatment visit. As a result, the analysis (as defined in the statistical analysis plan) only focused on a review of the adverse event data. Appendices attached to this synopsis style report aim to provide the relevant information.
Methodology: This was a multicenter, randomized, double-blind, 2-arm parallel group study comparing 20 mg rimonabant with placebo.
Number of patients: Planned: 720 Randomized: 165 Treated: 165
Evaluated: Safety : 165
Diagnosis and criteria for inclusion: Patients with a diagnosis of NASH (confirmed by central pathologist interpretation) by liver biopsy performed within the last 6 months were included in this study.
Investigational product: Rimonabant Dose: 20 mg tablet once daily Administration: Oral (before breakfast) Batch number(s): [redacted]

Duration of treatment: 24 months

Duration of observation: 28 months (including a 1 month screening period, 24 month double-blind treatment period, and 3 month posttreatment follow-up)

Reference therapy: Placebo

Dose: Not applicable

Administration: Oral (before breakfast)

Batch number(s): [redacted]

Criteria for evaluation:

Efficacy: Efficacy data were not analyzed for this study as liver biopsies were not performed at the end-of-treatment visit (ie, postbaseline assessments) at the time of premature stop of the study.

Safety: Only adverse events were reviewed and described.

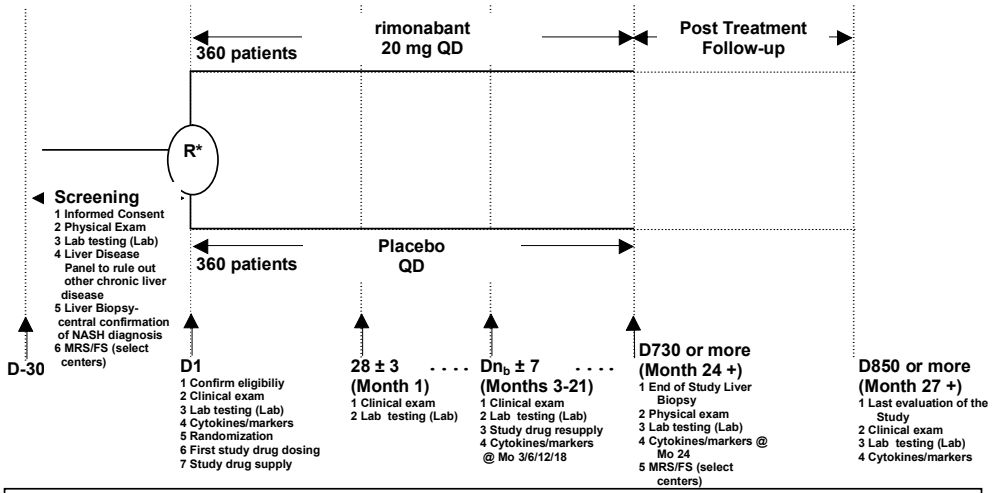
Statistical methods:

Efficacy: Not applicable

Safety: Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 11.1 and summarized by treatment group, using descriptive statistics.

Summary:

A summary of the study design is provided below, and a study flow-chart is provided after the synopsis.



Dn_b: treatment duration is flexible and defined by the timing of the last patient randomized; on-treatment visits will occur at months
1, 3, 6, 9, 12, 15, 18, 21 and 24, then every 3 months until the end of study liver biopsy is performed at Visit 12 (see Study Flowchart notes below)
Clinical Exam: Directed, interim physical and neuro/psych exam to include scripted neurological and psychiatric questions
Lab: (should be performed fasting) CBC with plts, electrolytes, AST, ALT, alkaline phosphatase, GGT, bilirubin, fasting total cholesterol, LDL, HDL, TG, FSG, fasting serum insulin, Prothrombin time/INR and Urinalysis at screening and end of DB treatment visit only
Liver Disease Panel (screen to rule out other chronic liver disease): HBsAg, anti-HBs, anti-HBc total, anti-HCV, anti-HIV (ELISA), anti-smooth muscle and anti-mitochondrial antibodies, PEP (albumin, α1-AT level, ceruloplasmin and IG), AFP, TSH, transferrin, iron, transferrin saturation, ferritin
Cytokines/markers: adiponectin. hyaluronate

Summary of populations: Table 1 summarizes the randomized and exposed populations.

Table 1 - Summary of patient populations - n(%) - randomized population

	Placebo	Rimonabant 20 mg	Overall
Randomized population	90 (100%)	75 (100%)	165 (100%)
Randomized and exposed population	90 (100%)	75 (100%)	165 (100%)

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

Patient disposition: All randomized patients were exposed to at least 1 dose of investigational product. None of the patients completed the study as planned. Most patients discontinued treatment as a result of premature stop of the study and were counted in the category "other reason". Table 2 summarizes patient disposition, including reasons for treatment discontinuation.

Table 2 - Summary of patient disposition - end-of-treatment - n(%) - randomized population

	Placebo (N=90)	Rimonabant 20 mg (N=75)
Patients randomized	90	75
Randomized but not treated	0	0
Randomized and treated	90 (100%)	75 (100%)
Completed study treatment period	0	0
Did not complete the study treatment period	90 (100%)	75 (100%)
Main reason for treatment discontinuation		
Adverse event	0	9 (12.0%)
Poor compliance to protocol	0	1 (1.3%)
Lost to follow-up	0	1 (1.3%)
Other reason	90 (100%)	64 (85.3%)
Subject status at the follow-up visit		
Alive	74 (82.2%)	60 (80.0%)
Dead	0	0
Lost to follow-up	0	1 (1.3%)
Missing	16 (17.8%)	14 (18.7%)

Note: % calculated using the number of randomized patients as denominator.
Category adverse event includes all AEs, TEAE or not.
"Missing" does not refer to missing patients. Information on the end of treatment was collected for all these patients. Missing pertains to missing information on the CRF page entitled "subject status", either because the Investigator crossed out the page or it was not collected.

Exposure: The safety population in this study included all 165 patients randomized and exposed to at least 1 dose of the investigational product. The mean number of days patients were exposed to the investigational products was similar in the 2 treatment groups (97.7 days for the 20 mg rimonabant group and 100 days for the placebo group). Patient exposure, based on the safety population, is presented in Table 3.

Table 3 - Summary of exposure to study drug - safety population

	Placebo (N=90)	Rimonabant 20 mg (N=75)
Extent of exposure (days)		
Number	90	75
Mean (SD)	100.0 (66.9)	97.7 (70.4)
Median	94.0	89.0
Min : Max	1 : 298	2 : 298
Count of patients [n(%)]		
1-30 days	17 (18.9%)	16 (21.3%)
31-90 days	27 (30.0%)	22 (29.3%)
91-180 days	36 (40.0%)	27 (36.0%)
> 180 days	10 (11.1%)	10 (13.3%)

Demographics: Patient demographic characteristics are presented in Table 4.

Table 4 - Summary of patient demographics at baseline - randomized population

	Placebo (N=90)	Rimonabant 20 mg (N=75)	Overall (N=165)
Age (years)			
Number	90	75	165
Mean (SD)	45.3 (11.6)	48.6 (12.1)	46.8 (11.9)
Median	46.5	50.0	48.0
Min : Max	22 : 71	18 : 72	18 : 72
[18-44]	41 (45.6%)	25 (33.3%)	66 (40.0%)
[45-64]	47 (52.2%)	44 (58.7%)	91 (55.2%)
≥ 65	2 (2.2%)	6 (8.0%)	8 (4.8%)
Gender [n (%)]			
Number	90	75	165
Male	43 (47.8%)	44 (58.7%)	87 (52.7%)
Female	47 (52.2%)	31 (41.3%)	78 (47.3%)
Race [n (%)]			
Number	90	75	165
Caucasian	86 (95.6%)	67 (89.3%)	153 (92.7%)
Black	1 (1.1%)	3 (4.0%)	4 (2.4%)
Asian, Oriental	2 (2.2%)	3 (4.0%)	5 (3.0%)
American Indian or Alaska Native	1 (1.1%)	1 (1.3%)	2 (1.2%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	1 (1.3%)	1 (0.6%)
Ethnicity in US			
Number	35	36	71
American Hispanic	9/ 35 (25.7%)	12/ 36 (33.3%)	21/ 71 (29.6%)
American non Hispanic	26/ 35 (74.3%)	24/ 36 (66.7%)	50/ 71 (70.4%)
Waist circumference (cm)			
Number	90	75	165
Mean (SD)	109.76 (14.53)	108.61 (13.90)	109.24 (14.21)
Median	108.50	107.30	108.00
Min : Max	73.0 : 143.5	79.0 : 151.0	73.0 : 151.0
For men			
≤ 102 cm	11 (25.6%)	7 (15.9%)	18 (20.7%)
> 102 cm	32 (74.4%)	37 (84.1%)	69 (79.3%)

	Placebo (N=90)	Rimonabant 20 mg (N=75)	Overall (N=165)
For women			
≤ 88 cm	3 (6.4%)	5 (16.1%)	8 (10.3%)
> 88 cm	44 (93.6%)	26 (83.9%)	70 (89.7%)
Weight (kg)			
Number	90	75	165
Mean (SD)	98.32 (21.67)	95.55 (20.38)	97.06 (21.07)
Median	94.85	91.80	94.00
Min : Max	64.7 : 157.8	61.2 : 157.5	61.2 : 157.8
BMI (kg/m^2)			
Number	90	75	165
Mean (SD)	34.49 (6.68)	33.13 (4.95)	33.87 (5.98)
Median	33.39	32.32	32.78
Min : Max	24.1 : 57.1	24.5 : 48.6	24.1 : 57.1
≤ 25	3 (3.3%)	1 (1.3%)	4 (2.4%)
]25-30[	25 (27.8%)	22 (29.3%)	47 (28.5%)
[30-35[	27 (30.0%)	29 (38.7%)	56 (33.9%)
[35-40[	21 (23.3%)	16 (21.3%)	37 (22.4%)
≥ 40	14 (15.6%)	7 (9.3%)	21 (12.7%)

Note: Number corresponds to the count of patients with non missing data used for the calculation of the percentage

Efficacy results : Not applicable

Safety results:

- **Overview of adverse events**

There were no deaths in this study. An overview of treatment emergent adverse events (TEAEs) experienced by patients with at least 1 TEAE is presented in Table 5.

Table 5 - Overview of TEAEs - safety population

	Placebo (N=90)	Rimonabant 20 mg (N=75)
Patients with any TEAE	49 (54.4%)	53 (70.7%)
Patients with any serious TEAE	3 (3.3%)	5 (6.7%)
Patients with any TEAE leading to death	0	0
Patients with TEAE leading to permanent treatment discontinuation	0	9 (12.0%)

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

- **Summary of TEAEs**

The most commonly reported TEAEs in the 20 mg rimonabant group belonged to the psychiatric disorders system organ class (SOC) (37.3% versus 13.3% in the placebo group), general disorders and administration site conditions (29.3% versus 17.8% in the placebo group), and gastrointestinal disorders (26.7% versus 17.8% in the placebo group). Treatment-emergent adverse events in the nervous system disorders SOC were reported with similar incidences in both treatment groups (see Table 6). All TEAEs are presented by SOC, high-level group term, high-level term, and preferred term (PT) in Appendix (reference not disclosed).

Table 6 Number (%) of patients experiencing at least 1 TEAE (cut-off: incidence of at least 5% in any treatment group): safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term	Placebo (N=90)	Rimonabant 20 mg (N=75)
Any Class	49 (54.4%)	53 (70.7%)
PSYCHIATRIC DISORDERS	12 (13.3%)	28 (37.3%)
Insomnia	3 (3.3%)	12 (16.0%)
Anxiety	6 (6.7%)	7 (9.3%)
Depressed Mood	2 (2.2%)	5 (6.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (17.8%)	22 (29.3%)
Fatigue	5 (5.6%)	11 (14.7%)
Irritability	7 (7.8%)	9 (12.0%)
Asthenia	0	4 (5.3%)
GASTROINTESTINAL DISORDERS	16 (17.8%)	20 (26.7%)
Diarrhoea	5 (5.6%)	7 (9.3%)
Nausea	5 (5.6%)	7 (9.3%)
NERVOUS SYSTEM DISORDERS	20 (22.2%)	19 (25.3%)
Dizziness	7 (7.8%)	10 (13.3%)
Disturbance In Attention	2 (2.2%)	5 (6.7%)
Headache	9 (10.0%)	2 (2.7%)
METABOLISM AND NUTRITION DISORDERS	7 (7.8%)	10 (13.3%)
Decreased Appetite	1 (1.1%)	8 (10.7%)

Only rows with frequency of at least 5% in at least one column are shown
Note: Table sorted by decreasing incidence of Primary SOC and PT within SOC. Sorting based on results for Rimonabant 20 mg arm. In case of equal frequency regarding SOC, alphabetical order is used.

- **Summary of serious adverse events**

Few serious adverse events were reported during this study. The incidence of serious adverse events was higher in the 20 mg rimonabant group (5/75 [6.7%]) than in the placebo group (3/90 [3.3%]). Two patients in the 20 mg rimonabant group reported adverse events of special interest (suicidal ideation and hallucination, respectively), which were reported, by convention, as serious adverse events (seeTable 7). No patients reported suicidal behavior.

Results of the Columbia-suicide severity rating scale (C-SSRS) are presented in tables in Appendix (reference not disclosed) and case report form pages for patients with a positive C-SSRS during the study are provided in Appendix (reference not disclosed).

Table 7 Number (%) of patients experiencing at least 1 serious TEAE - safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term	Placebo (N=90)	Rimonabant 20 mg (N=75)
Any Class	3 (3.3%)	5 (6.7%)
PSYCHIATRIC DISORDERS	0	2 (2.7%)
Hallucination	0	1 (1.3%)
Suicidal Ideation	0	1 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (1.1%)	0
Chest Pain	1 (1.1%)	0
GASTROINTESTINAL DISORDERS	1 (1.1%)	1 (1.3%)
Abdominal Pain	1 (1.1%)	1 (1.3%)
INFECTIONS AND INFESTATIONS	1 (1.1%)	1 (1.3%)
Wound Infection Staphylococcal	0	1 (1.3%)
Pyelonephritis Acute	1 (1.1%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (1.3%)
Musculoskeletal Chest Pain	0	1 (1.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.1%)	0
Seroma	1 (1.1%)	0
CARDIAC DISORDERS	1 (1.1%)	0
Atrial Fibrillation	1 (1.1%)	0
RENAL AND URINARY DISORDERS	0	1 (1.3%)
Renal Failure Acute	0	1 (1.3%)

Note: Table sorted by decreasing incidence of Primary SOC and PT within SOC. Sorting based on results for Rimonabant 20 mg arm. In case of equal frequency regarding SOC, alphabetical order is used.

- **Summary of Deaths**

There were no deaths in this study.

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

Discontinuations due to TEAEs were reported in the 20 mg rimonabant group only. A total of 9 patients discontinued due to TEAEs. The most commonly reported TEAEs that resulted in discontinuation belonged to the psychiatric disorders SOC (7/75 [9.3%]). Other SOCs that had TEAEs cited by more than 2 patients included gastrointestinal disorders (4/ 75 [5.3%]), general disorders and administration site conditions (3/ 75 [4.0%]), and nervous system disorders (3/75 [4.0%]) (see Table 8).

Table 8 Number (%) of patients experiencing at least 1 TEAE resulting in permanent treatment discontinuation - safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term	Placebo (N=90)	Rimonabant 20 mg (N=75)
Any Class	0	9 (12.0%)
PSYCHIATRIC DISORDERS	0	7 (9.3%)
Insomnia	0	2 (2.7%)
Anxiety	0	1 (1.3%)
Depressed Mood	0	1 (1.3%)
Depression	0	1 (1.3%)
Delirium	0	1 (1.3%)
Hallucination	0	1 (1.3%)
Sleep Disorder Due To General Medical Condition, Insomnia Type	0	1 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	3 (4.0%)
Fatigue	0	1 (1.3%)
Irritability	0	1 (1.3%)
Asthenia	0	1 (1.3%)
GASTROINTESTINAL DISORDERS	0	4 (5.3%)
Diarrhoea	0	1 (1.3%)
Nausea	0	4 (5.3%)
Constipation	0	1 (1.3%)
Vomiting	0	1 (1.3%)
NERVOUS SYSTEM DISORDERS	0	3 (4.0%)
Disturbance In Attention	0	2 (2.7%)
Headache	0	1 (1.3%)
Somnolence	0	1 (1.3%)
Tremor	0	1 (1.3%)
INFECTIONS AND INFESTATIONS	0	1 (1.3%)
Wound Infection Staphylococcal	0	1 (1.3%)
METABOLISM AND NUTRITION DISORDERS	0	1 (1.3%)
Hypoalbuminaemia	0	1 (1.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (1.3%)
Myalgia	0	1 (1.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (1.3%)
Procedural Pain	0	1 (1.3%)

PRIMARY SYSTEM ORGAN CLASS Preferred Term	Placebo (N=90)	Rimonabant 20 mg (N=75)
CARDIAC DISORDERS	0	1 (1.3%)
Palpitations	0	1 (1.3%)
EYE DISORDERS	0	1 (1.3%)
Diplopia	0	1 (1.3%)
VASCULAR DISORDERS	0	1 (1.3%)
Hypotension	0	1 (1.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	2 (2.7%)
Haemorrhagic Anaemia	0	1 (1.3%)
Thrombocytopenia	0	1 (1.3%)

Note: Table sorted by decreasing incidence of Primary SOC and PT within SOC. Sorting based on results for Rimonabant 20 mg arm. In case of equal frequency regarding SOC, alphabetical order is used.

Conclusions: [redacted]

Date of report: 24-June-2009