SYNOPSIS

Title of the study: A double-blind, randomized, placebo-controlled, parallel group study of rimonabant 20 mg daily for the treatment of type 2 diabetic patients with nonalcoholic steatohepatitis (NASH) (EFC10144)

Investigators: No Principal Investigator was planned or identified for this study

Study centers: The study was conducted at 41 centers in 12 countries (Argentina, Australia, Belgium, Italy, Mexico, Poland, Portugal, Puerto Rico, Romania, Spain, the United Kingdom, and the United States of America).

Publications (reference): None

Study period:

Date first patient enrolled: 19 February 2008

Date last patient completed: 23 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 type 2 diabetic patients. The objectives of the protocol were as follows:

Primary: To demonstrate, in patients with comorbid type 2 diabetes following a minimum of 18 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 with comorbid type 2 diabetes following a minimum of 18 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 aminotransferase (AST)/ alanine aminotransferase (ALT) level.

The study was stopped prematurely after 89 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: 89 Treated: 88

Evaluated: Safety: 88

Diagnosis and criteria for inclusion: Patients with a diagnosis of type 2 diabetes of at least 6 months duration diagnosed by fasting plasma glucose $\geq$126 mg/dl or 2-hour post load glucose of $\geq$200 mg/dl during an oral glucose tolerance test, and 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: 18 months

Duration of observation: 22 months (including a 1 month screening period, 18 month double-blind treatment period, and 3 month post-treatment 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.

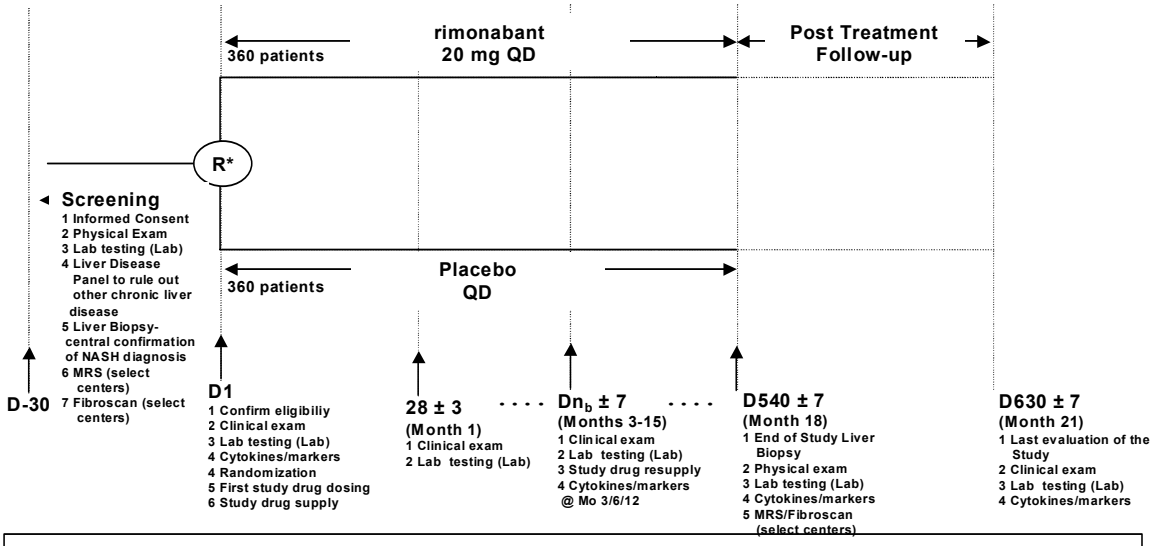
Statistical methods:

Efficacy: Not applicable

Safety: Adverse events were coded using 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 18 months; on-treatment visits will occur at months 1, 3, 6, 9, 12 and 15 and the end of study liver biopsy is performed prior to the end of double-blind treatment visit at Month 18
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	49 (100%)	40 (100%)	89 (100%)
Randomized and exposed population	48 (98.0%)	40 (100%)	88 (98.9%)

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

Patient disposition: A total of 88 randomized patients were exposed to at least 1 dose of investigational product. One patient from the placebo group was randomized, but not exposed to 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=49)	Rimonabant 20 mg (N=40)
Patients randomized	49	40
Randomized but not treated	1 (2.0%)	0
Randomized and treated	48 (98.0%)	40 (100%)
Completed study treatment period	0	0
Did not complete the study treatment period	48 (98.0%)	40 (100%)
Main reason for treatment discontinuation		
Adverse event	1 (2.0%)	3 (7.5%)
Poor compliance to protocol	0	0
Lost to follow-up	0	0
Other reason	47 (95.9%)	37 (92.5%)
Subject status at the follow-up visit		
Alive	30 (61.2%)	32 (80.0%)
Dead	0	0
Lost to follow-up	1 (2.0%)	0
Missing	18 (36.7%)	8 (20.0%)

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 88 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 (90.6 days for the 20 mg rimonabant group and 89.7 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=48)	Rimonabant 20 mg (N=40)
Extent of exposure (days)		
Number	48	40
Mean (SD)	89.7 (60.3)	90.6 (65.8)
Median	80.0	77.5
Min : Max	7 : 265	2 : 227
Count of patients [n(%)]		
1-30 days	9 (18.8%)	8 (20.0%)
31-90 days	17 (35.4%)	15 (37.5%)
91-180 days	19 (39.6%)	11 (27.5%)
> 180 days	3 (6.3%)	6 (15.0%)

Demographics: Patient demographic characteristics are presented in Table 4.

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

	Placebo (N=49)	Rimonabant 20 mg (N=40)	Overall (N=89)
Age (years)			
Number	49	40	89
Mean (SD)	53.0 (8.1)	52.9 (8.2)	53.0 (8.1)
Median	54.0	54.0	54.0
Min : Max	29 : 67	34 : 67	29 : 67
[18-44]	6 (12.2%)	7 (17.5%)	13 (14.6%)
[45-64]	42 (85.7%)	31 (77.5%)	73 (82.0%)
≥ 65	1 (2.0%)	2 (5.0%)	3 (3.4%)
Gender [n (%)]			
Number	49	40	89
Male	22 (44.9%)	19 (47.5%)	41 (46.1%)
Female	27 (55.1%)	21 (52.5%)	48 (53.9%)
Race [n (%)]			
Number	49	40	89
Caucasian	45 (91.8%)	38 (95.0%)	83 (93.3%)
Black	0	1 (2.5%)	1 (1.1%)
Asian, Oriental	2 (4.1%)	0	2 (2.2%)
American Indian or Alaska Native	1 (2.0%)	1 (2.5%)	2 (2.2%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (2.0%)	0	1 (1.1%)

	Placebo (N=49)	Rimonabant 20 mg (N=40)	Overall (N=89)
Ethnicity in US			
Number	18	16	34
American Hispanic	4/ 18 (22.2%)	4/ 16 (25%)	8/ 34 (23.5%)
American non Hispanic	14/ 18 (77.8%)	12/ 16 (75%)	26/ 34 (76.5%)
Waist circumference (cm)			
Number	49	40	89
Mean (SD)	111.80 (19.19)	112.51 (12.35)	112.12 (16.39)
Median	107.90	112.50	110.00
Min : Max	83.1 : 200.0	90.0 : 141.0	83.1 : 200.0
For men			
≤ 102 cm	4 (18.2%)	3 (15.8%)	7 (17.1%)
> 102 cm	18 (81.8%)	16 (84.2%)	34 (82.9%)
For women			
≤ 88 cm	1 (3.7%)	0	1 (2.1%)
> 88 cm	26 (96.3%)	21 (100%)	47 (97.9%)
Weight (kg)			
Number	49	40	89
Mean (SD)	93.76 (17.25)	98.58 (17.44)	95.92 (17.40)
Median	92.00	99.80	93.00
Min : Max	65.1 : 147.8	64.4 : 133.5	64.4 : 147.8
BMI (kg/m^2)			
Number	49	40	89
Mean (SD)	34.42 (6.56)	34.87 (5.11)	34.63 (5.92)
Median	33.77	35.11	34.34
Min : Max	24.0 : 57.0	24.5 : 46.3	24.0 : 57.0
≤ 25	1 (2.0%)	1 (2.5%)	2 (2.2%)
]25-30[	10 (20.4%)	5 (12.5%)	15 (16.9%)
[30-35[	21 (42.9%)	13 (32.5%)	34 (38.2%)
[35-40[	10 (20.4%)	14 (35.0%)	24 (27.0%)
≥ 40	7 (14.3%)	7 (17.5%)	14 (15.7%)

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 TEAEs experienced by patients with at least 1 TEAE is presented in Table 5.

Table 5 - Overview of TEAEs - safety population

	Placebo (N=48)	Rimonabant 20 mg (N=40)
Patients with any TEAE	30 (62.5%)	23 (57.5%)
Patients with any serious TEAE	2 (4.2%)	1 (2.5%)
Patients with any TEAE leading to death	0	0
Patients with TEAE leading to permanent treatment discontinuation	1 (2.1%)	3 (7.5%)

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 treatment-emergent adverse events**

The most commonly reported TEAEs in the 20 mg rimonabant group belonged to the psychiatric disorders system organ class (SOC) (30.0% versus 16.7% in the placebo group). Treatment-emergent adverse events in the nervous system disorders SOC and the infections and infestations SOC were reported with similar incidences in both treatment groups (see Table 6). All TEAEs are presented by SOC, HLGT, HLT, and PT.

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=48)	Rimonabant 20 mg (N=40)
Any Class	30 (62.5%)	23 (57.5%)
PSYCHIATRIC DISORDERS	8 (16.7%)	12 (30.0%)
Anxiety	3 (6.3%)	7 (17.5%)
Depressed Mood	2 (4.2%)	3 (7.5%)
Depression	1 (2.1%)	3 (7.5%)
GASTROINTESTINAL DISORDERS	13 (27.1%)	9 (22.5%)
Diarrhoea	4 (8.3%)	5 (12.5%)
Nausea	4 (8.3%)	3 (7.5%)
INFECTIONS AND INFESTATIONS	9 (18.8%)	7 (17.5%)
Nasopharyngitis	2 (4.2%)	2 (5.0%)
METABOLISM AND NUTRITION DISORDERS	10 (20.8%)	6 (15.0%)
Decreased Appetite	3 (6.3%)	3 (7.5%)
Anorexia	0	2 (5.0%)
Increased Appetite	5 (10.4%)	0

PRIMARY SYSTEM ORGAN CLASS Preferred Term	Placebo (N=48)	Rimonabant 20 mg (N=40)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9 (18.8%)	6 (15.0%)
Irritability	3 (6.3%)	4 (10.0%)
Fatigue	5 (10.4%)	0
NERVOUS SYSTEM DISORDERS	6 (12.5%)	4 (10.0%)
Dizziness	2 (4.2%)	2 (5.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	9 (18.8%)	2 (5.0%)
Muscle Spasms	3 (6.3%)	0

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. One patient in the placebo group experienced suicidal ideation, which was reported, by convention, as a serious adverse event. No patients reported suicidal behavior. Please refer to the CSR Appendix for details presented in the narratives.

Results of the Columbia-suicide severity rating scale (C-SSRS) are presented in tables in the CSR Appendix and case report form pages for patients with a positive C-SSRS during the study are provided in the CSR Appendix.

- **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 for 3 patients in the rimonabant group compared with 1 patient in the placebo group. In the rimonabant group TEAEs of anxiety, diarrhea, bronchitis, dizziness, trigeminal neuralgia, and vertigo were cited as reasons for discontinuation. In the placebo group, the patient who discontinued reported decreased interest as the reason for discontinuation. The corresponding summary table is presented in the CSR Appendix.

Conclusions: [redacted]

Date of report: 24-June-2009