SYNOPSIS

Title of the study:	A randomized, double-blind, parallel-group, multicenter, multinational study to assess glycemic control with rimonabant in comparison with glimepiride over 1 year in overweight/obese type 2 diabetic patients not adequately controlled with metformin (EFC10007)
Investigators:	No Principal Investigator was planned or identified for this study
Study centers:	The study was conducted at 101 centers in 14 countries (Chile, Denmark, Finland, Hungary, India, Italy, Republic of Korea, Mexico, Puerto Rico, Romania, Russian Federation, Spain, Sweden, and the United States of America)
Publications (reference):	None
Study period:	
Date first patient enrolled:	16 March 2007
Date last patient completed:	04 March 2009
Phase of development:	Phase 3b

Objectives: The objectives of the protocol were as follows:

Primary: To demonstrate, after 52 weeks (1 year) of treatment, the non-inferiority of rimonabant 20 mg once daily (OD) versus glimepiride OD in reducing glycosylated hemoglobin A1c (HbA_{1c}) in overweight/obese patients with type 2 diabetes not adequately controlled with metformin at a stable dose (≥1500mg/day) for at least 3 months.

Secondary:

- To assess the effect of rimonabant in comparison to glimepiride after 52 weeks (1 year) of treatment on body weight, high-density lipoprotein cholesterol, waist circumference, triglycerides, other markers of glycemic control (fasting glucose, fasting-insulin, C-peptide).
- To evaluate the long-term safety and tolerability of rimonabant in comparison with glimepiride in patients with type 2 diabetes not adequately controlled with metformin.

The study was stopped prematurely after all patients had been randomized (508 patients), 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, and on the primary efficacy criterion. As a result, the analysis (as defined in the statistical analysis plan) only focused on these data 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 comparing rimonabant 20 mg with glimepiride (from 1 mg up to 6 mg) in patients with type 2 diabetes. The treatment period included a 12-week forced dose titration (up to the maximal dose of 6 mg/day or up to the maximal tolerated dose for glimepiride) and a 40-week maintenance period.

Number of patients:	Planned: 500	Randomized: 508	Treated: 505
Evaluated:	Efficacy (modified intent-to-treat [mITT]): 482	Safety : 505	

Diagnosis and criteria for inclusion: Male or female patients with legal age, body mass index (BMI) >27 kg/m², type 2 diabetes as defined by World Health Organization criteria (diagnosis was based on fasting venous plasma glucose concentration ≥7.0 mmol/L or 2-hour postglucose load venous plasma glucose ≥11.1 mmol/L) only treated with metformin at a stable dose ≥1500 mg/day for at least 3 months, HbA_{1c} ≥7% and ≤9% at screening, and ability to perform blood glucose self-monitoring confirmed at baseline were included in the study.

Investigational product: Rimonabant 20 mg tablet (or matched placebo)

Dose: 20 mg tablet od

Administration: Oral (before breakfast)

Batch numbers: [redacted]

Duration of treatment: 52 weeks (1 year)

Duration of observation: Approximately 65 weeks (including a 2-week screening period, 52-week double-blind treatment period, and 75-day post-treatment follow-up)

Reference therapy: Glimepiride 1, 2, and 4 mg tablets (or matched placebo)

Dose: 1 to 6 mg od

Administration: Oral (before breakfast)

Batch numbers: [redacted]

Criteria for evaluation:

Efficacy: Only the primary criterion was analyzed: absolute change in HbA_{1c} from baseline to Week 52 visit.

Safety: Only adverse events were reviewed and described.

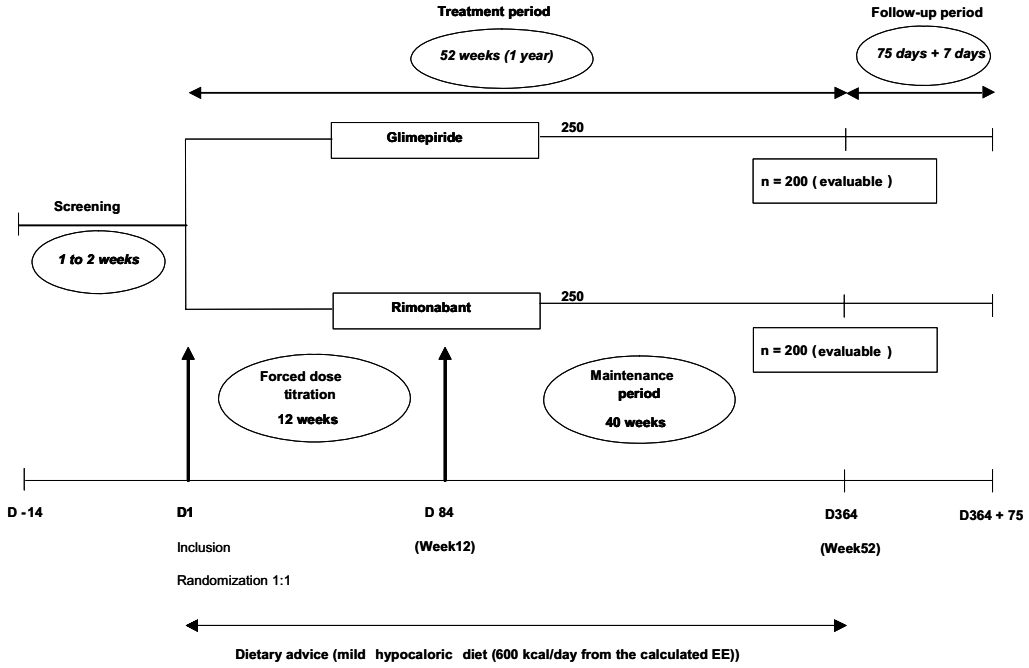
Statistical methods:

Efficacy: The change in HbA_{1c} from baseline to Week 52, was analyzed using a Mixed Model for Repeated Measurements, with treatment (rimonabant 20 mg or glimepiride), visit, randomization stratum ($7\% \leq HbA_{1c} < 8\%$ or $8\% \leq HbA_{1c} \leq 9\%$), treatment by-visit interaction, stratum-by-visit interaction, and centered baseline as covariates. Non-inferiority of rimonabant 20 mg to glimepiride was to be demonstrated if the 95% confidence interval (CI) upper bound for the difference (rimonabant - glimepiride) in the adjusted mean changes from baseline to Week 52 for HbA_{1c} was less than or equal to 0.4%. The primary efficacy analysis was performed in the mITT population, ie randomized patients who were exposed and had baseline and postbaseline assessments, who completed at least 6 months of study treatment (Visit 11). This population was chosen for the analysis because of the difference in the onset of action of rimonabant and glimepiride. In addition, data obtained after the introduction of anti-diabetic rescue medication were excluded.

Safety: Adverse events were coded according to 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 (per protocol amendments) is provided in Figure 1 after the synopsis.



Summary of populations: Table 1 summarizes the analyzed populations.

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

	Glimepiride (N=253)	SR141716 20 mg (N=255)	Overall (N=508)
Randomized population	253 (100%)	255 (100%)	508 (100%)
Randomized and exposed population (safety population)	252 (99.6%)	253 (99.2%)	505 (99.4%)
mITT population	244 (96.4%)	238 (93.3%)	482 (94.9%)

Patient disposition: All randomized patients were exposed to at least 1 dose of investigational product, except 2 patients in the rimonabant group and 1 patient in the glimepiride group who were not treated. In both treatment groups, 41 patients (about 16%) 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 2 summarizes patient disposition including reasons for treatment discontinuation.

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

	Glimepiride (N=253)	SR141716 20 mg (N=255)
Patients randomized	253 (100%)	255 (100%)
Randomized but not treated	1 (0.4%)	2 (0.8%)
Randomized and treated	252 (99.6%)	253 (99.2%)
Completed study treatment period	41 (16.2%)	41 (16.1%)
Did not complete study treatment period	207 (81.8%)	207 (81.2%)
Missing	4 (1.6%)	5 (2.0%)
Main reason for treatment discontinuation		
Lack of efficacy	2 (0.8%)	2 (0.8%)
Adverse event	10 (4.0%)	21 (8.2%)
Subject's request	10 (4.0%)	13 (5.1%)
Poor compliance to protocol	2 (0.8%)	5 (2.0%)
Subject lost to follow-up	2 (0.8%)	1 (0.4%)
Other reason	181 (71.5%)	165 (64.7%)

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

Category adverse event includes all adverse events (AEs), treatment-emergent AEs (TEAE) or not.

Missing: 9 randomized patients were discontinued from a single center, which was closed due to noncompliance with Good Clinical Practices (GCPs). For these patients, all available data were collected but only safety data have been analyzed.

Exposure: The safety population in this study included 505 patients randomized and exposed to at least 1 dose of the investigational product. The mean number of days the patients were exposed to the investigational products was 229.6 days in the 20 mg rimonabant group and 238.1 days in the glimepiride group. In the glimepiride group, the mean (SD) dose of glimepiride was 4.4 (1.8) mg/day at the end of the titration period, as well as at the end of the maintenance period. Patient exposure, based on the safety population, is presented in Table 3.

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

	Glimepiride (N=252)	SR141716 20 mg (N=253)
Cumulative exposure (patient years)	164.2	159.1
Extent of exposure (days)		
Number	252	253
Mean (SD)	238.1 (88.8)	229.6 (98.1)
Median	237.0	226.0
Min : Max	4 : 373	2 : 392
Count of patients [n(%)]		
1 - 28 days	5 (2.0%)	8 (3.2%)
29 - 84 days	10 (4.0%)	14 (5.5%)
85 - 168 days	32 (12.7%)	37 (14.6%)
169 - 224 days	64 (25.4%)	63 (24.9%)
225 - 364 days	121 (48.0%)	115 (45.5%)
≥ 365 days	20 (7.9%)	16 (6.3%)

Demographics: Patient demographic characteristics are presented in Table 4.

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

	Glimepiride (N=253)	SR141716 20 mg (N=255)	All (N=508)
Age (years)			
Number	253	255	508
Mean (SD)	54.7 (9.9)	53.0 (10.1)	53.8 (10.0)
Median	56.0	54.0	55.0
Min : Max	26 : 79	27 : 76	26 : 79
[18-44]	38 (15.0%)	54 (21.2%)	92 (18.1%)
[45-64]	178 (70.4%)	171 (67.1%)	349 (68.7%)
≥ 65	37 (14.6%)	30 (11.8%)	67 (13.2%)
Gender			
Number	253	255	508
Male	121 (47.8%)	107 (42.0%)	228 (44.9%)
Female	132 (52.2%)	148 (58.0%)	280 (55.1%)
Race			
Number	253	255	508
Caucasian/White	210 (83.0%)	212 (83.1%)	422 (83.1%)
Black	10 (4.0%)	12 (4.7%)	22 (4.3%)
Asian/Oriental	29 (11.5%)	29 (11.4%)	58 (11.4%)
Other	4 (1.6%)	2 (0.8%)	6 (1.2%)
Ethnicity in US			
Number	58	63	121
American Hispanic	7/58 (12.1%)	5/63 (7.9%)	12/121 (9.9%)
American non Hispanic	51/58 (87.9%)	58/63 (92.1%)	109/121 (90.1%)
Waist circumference (cm)			
Number	251	251	502
Mean (SD)	113.8 (16.3)	112.1 (14.4)	113.0 (15.4)
Median	111.5	109.8	110.6
Min : Max	88 : 199	87 : 165	87 : 199
For men			
≤ 102 cm	19/120 (15.8%)	24/105 (22.9%)	43/225 (19.1%)
> 102 cm	101/120 (84.2%)	81/105 (77.1%)	182/225 (80.9%)
For women			
≤ 88 cm	0/131	1/146 (0.7%)	1/277 (0.4%)
> 88 cm	131/131 (100%)	145/146 (99.3%)	276/277 (99.6%)
Height (cm)			
Number	252	253	505
Mean (SD)	166.0 (11.0)	164.6 (11.4)	165.3 (11.2)
Median	165.5	164.0	165.0
Min : Max	135 : 198	132 : 195	132 : 198
Weight (kg)			
Number	252	253	505
Mean (SD)	98.4 (25.6)	95.5 (21.2)	96.9 (23.5)
Median	92.8	92.0	92.2
Min : Max	50 : 223	48 : 179	48 : 223

	Glimepiride (N=253)	SR141716 20 mg (N=255)	All (N=508)
BMI (kg/m^2)			
Number	252	253	505
Mean (SD)	35.5 (7.2)	35.1 (6.0)	35.3 (6.6)
Median	33.4	34.3	33.9
Min : Max	27 : 79	26 : 61	26 : 79
< 27	1 (0.4%)	3 (1.2%)	4 (0.8%)
[27-30[	51 (20.2%)	54 (21.3%)	105 (20.8%)
[30-35[	94 (37.3%)	81 (32.0%)	175 (34.7%)
[35-40[	54 (21.4%)	63 (24.9%)	117 (23.2%)
≥ 40	52 (20.6%)	52 (20.6%)	104 (20.6%)
HbA_{1c} at screening			
Number	253	255	508
≥ 7.0% to < 8.0%	150 (59.3%)	149 (58.4%)	299 (58.9%)
≥ 8.0% to ≤ 9.0%	103 (40.7%)	106 (41.6%)	209 (41.1%)

Efficacy results: Mean HbA_{1c} values in both treatment groups were comparable at baseline. The 95% CI upper bound for the mean difference of the absolute change in HbA_{1c} from baseline to Week 52 in the rimonabant group versus the glimepiride group was lower than the predefined non-inferiority margin of 0.4% (Table 5). These results demonstrated the non-inferiority of treatment with rimonabant 20 mg compared with glimepiride in reducing HbA_{1c}.

Table 5 – Mean change and mean difference from baseline in HbA_{1c} at Week 52 - mITT population

HbA_{1c}(%)	Glimepiride (N=244)	SR141716 20 mg (N=238)
Baseline		
Number	220	208
Mean (SD)	7.85 (0.60)	7.88 (0.58)
Median	7.80	7.80
Min : Max	7.0 : 9.0	7.0 : 9.0
Week 52		
Number	220	208
Mean (SD)	6.89 (0.85)	6.93 (1.08)
Median	6.80	6.70
Min : Max	5.3 : 10.0	5.1 : 12.7
Change from baseline		
Number	220	208
Mean (SD)	-0.96 (0.89)	-0.95 (1.05)
Median	-1.00	-1.00
Min : Max	-3.6 : 1.4	-3.4 : 3.7
LSMean (SE)[a]	-0.84 (0.077)	-0.92 (0.081)
LSMean difference vs GLIMEPIRIDE[a]		
Estimate (SE)		-0.08 (0.109)
95% CI		(-0.298 to 0.132)

(a): Mixed Model for Repeated Measurements

Safety results:

- **Overview of adverse events**

An overview of patients with at least 1 treatment-emergent adverse event (TEAE) is presented in Table 6. The incidence of serious TEAEs was comparable between the 2 treatment groups. There was 1 death in each group.

Table 6 – Overview of TEAEs - safety population

	Glimepiride (N=252)	SR141716 20 mg (N=253)
Patients with any TEAE	178 (70.6%)	162 (64.0%)
Patients with any serious TEAE	14 (5.6%)	13 (5.1%)
Patients with any TEAE leading to death	1 (0.4%)	1 (0.4%)
Patients with TEAE leading to permanent treatment discontinuation	10 (4.0%)	21 (8.3%)

Notes: TEAE: Treatment-Emergent Adverse Event
TEAE includes all adverse events (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**

Among the TEAEs reported in at least 5% of patients, the more frequently reported preferred terms (PTs) in the 20 mg rimonabant group compared with the glimepiride group were nausea, diarrhea, anxiety, and paraesthesia. Conversely, the more frequently reported PTs in the glimepiride group compared with 20 mg rimonabant were hypoglycaemia, dizziness, and headache (see Table 7). All TEAEs are presented by system organ class (SOC), high level group term, high level term, and PT in Appendix (not disclosed).

Table 7 – Number (%) of patients experiencing at least 1 TEAE (cut-off: incidence ≥5% in any treatment group) - safety population

Primary System Organ Class Preferred term	Glimepiride (N=252)	SR141716 20 mg (N=253)
Any Class	178 (70.6%)	162 (64.0%)
Infections and infestations	69 (27.4%)	62 (24.5%)
Nasopharyngitis	20 (7.9%)	18 (7.1%)
Nervous system disorders	54 (21.4%)	54 (21.3%)
Dizziness	20 (7.9%)	17 (6.7%)
Paraesthesia	3 (1.2%)	14 (5.5%)
Headache	19 (7.5%)	10 (4.0%)
Gastrointestinal disorders	44 (17.5%)	50 (19.8%)
Nausea	10 (4.0%)	23 (9.1%)
Diarrhoea	12 (4.8%)	17 (6.7%)
Psychiatric disorders	33 (13.1%)	43 (17.0%)
Anxiety	10 (4.0%)	17 (6.7%)
Metabolism and nutrition disorders	92 (36.5%)	28 (11.1%)
Hypoglycaemia	83 (32.9%)	24 (9.5%)

Notes: TEAE: Treatment-Emergent Adverse Event
TEAE includes all adverse events (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. 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**

The incidence of serious adverse event was similar in both groups (Table 8). One patient in each treatment group reported suicidal ideation, which was reported by convention as a serious adverse event. In the rimonabant group, suicidal ideation led to treatment discontinuation. No patients reported suicidal behavior.

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

Table 8 – Number (%) of patients experiencing at least 1 serious TEAE - safety population

Primary System Organ Class Preferred term	Glimepiride (N=252)	SR141716 20 mg (N=253)
Any Class	14 (5.6%)	13 (5.1%)
Infections and infestations	1 (0.4%)	1 (0.4%)
Cellulitis staphylococcal	0	1 (0.4%)
Anal abscess	1 (0.4%)	0
Nervous system disorders	3 (1.2%)	3 (1.2%)
Loss of consciousness	0	1 (0.4%)
Carotid artery stenosis	1 (0.4%)	0
Convulsion	0	1 (0.4%)
Ischaemic stroke	0	1 (0.4%)
Presyncope	1 (0.4%)	0
Carotid arteriosclerosis	1 (0.4%)	0
Haemorrhagic stroke	1 (0.4%)	0
Nystagmus	1 (0.4%)	0
Gastrointestinal disorders	0	2 (0.8%)
Oesophagitis	0	1 (0.4%)
Small intestinal obstruction	0	1 (0.4%)
Psychiatric disorders	1 (0.4%)	2 (0.8%)
Depressed mood	0	1 (0.4%)
Suicidal ideation	1 (0.4%)	1 (0.4%)
Musculoskeletal and connective tissue disorders	1 (0.4%)	2 (0.8%)
Muscular weakness	0	1 (0.4%)
Osteoarthritis	1 (0.4%)	1 (0.4%)
Metabolism and nutrition disorders	3 (1.2%)	1 (0.4%)
Hypoglycaemia	1 (0.4%)	1 (0.4%)
Hyperglycaemia	1 (0.4%)	0
Hypoglycaemic unconsciousness	1 (0.4%)	0
Injury, poisoning and procedural complications	1 (0.4%)	0
Lower limb fracture	1 (0.4%)	0
General disorders and administration site conditions	1 (0.4%)	0
Chest discomfort	1 (0.4%)	0
Cardiac disorders	2 (0.8%)	2 (0.8%)
Congestive cardiomyopathy	0	1 (0.4%)
Myocardial ischaemia	0	1 (0.4%)
Cardiac failure	1 (0.4%)	0
Coronary artery disease	1 (0.4%)	0

Primary System Organ Class Preferred term	Glimepiride (N=252)	SR141716 20 mg (N=253)
Vascular disorders	2 (0.8%)	0
Hypertension	1 (0.4%)	0
Hypertensive crisis	1 (0.4%)	0
Renal and urinary disorders	1 (0.4%)	0
Renal failure	1 (0.4%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4%)	1 (0.4%)
Uterine leiomyoma	0	1 (0.4%)
Non-small cell lung cancer	1 (0.4%)	0
Hepatobiliary disorders	1 (0.4%)	0
Bile duct stone	1 (0.4%)	0
Immune system disorders	1 (0.4%)	0
Drug hypersensitivity	1 (0.4%)	0

Notes: TEAE: Treatment-Emergent Adverse Event
TEAE includes all adverse event (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. 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 2 deaths in this study. In the rimonabant group, one patient died from congestive cardiomyopathy while on treatment, and in the glimepiride group, one patient died from haemorrhagic stroke 7 weeks after discontinuation of the investigational product.

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

Discontinuation of treatment due to TEAEs occurred in 21/253 patients (8.3%) in the rimonabant group compared with 10/252 patients (4.0%) in the glimepiride group. Table 8 summarizes these events by SOC and PT.

Table 8 – Number (%) of patients experiencing at least 1 TEAE leading to permanent treatment discontinuation - safety population

Primary System Organ Class Preferred term	Glimepiride (N=252)	SR141716 20 mg (N=253)
Any Class	10 (4.0%)	21 (8.3%)
Infections and infestations	1 (0.4%)	0
Urinary tract infection	1 (0.4%)	0
Nervous system disorders	2 (0.8%)	5 (2.0%)
Dizziness	1 (0.4%)	0
Hypoaesthesia	0	1 (0.4%)
Memory impairment	0	1 (0.4%)
Somnolence	0	1 (0.4%)
Tremor	0	1 (0.4%)
Parosmia	0	1 (0.4%)
Amnesia	0	1 (0.4%)
Ischaemic stroke	0	1 (0.4%)
Nystagmus	1 (0.4%)	0
Sensory loss	1 (0.4%)	0

Primary System Organ Class Preferred term	Glimepiride (N=252)	SR141716 20 mg (N=253)
Gastrointestinal disorders	0	4 (1.6%)
Nausea	0	1 (0.4%)
Diarrhoea	0	1 (0.4%)
Gastritis	0	1 (0.4%)
Abdominal pain upper	0	1 (0.4%)
Psychiatric disorders	3 (1.2%)	9 (3.6%)
Anxiety	2 (0.8%)	2 (0.8%)
Depressed mood	1 (0.4%)	1 (0.4%)
Insomnia	0	1 (0.4%)
Depression	1 (0.4%)	2 (0.8%)
Anger	1 (0.4%)	1 (0.4%)
Nightmare	0	1 (0.4%)
Suicidal ideation	0	1 (0.4%)
Parasomnia	0	1 (0.4%)
Psychosomatic disease	0	1 (0.4%)
Abnormal dreams	1 (0.4%)	0
Musculoskeletal and connective tissue disorders	0	4 (1.6%)
Muscular weakness	0	2 (0.8%)
Myalgia	0	1 (0.4%)
Muscle spasms	0	1 (0.4%)
Sensation of heaviness	0	1 (0.4%)
Metabolism and nutrition disorders	3 (1.2%)	0
Hypoglycaemia	1 (0.4%)	0
Hyperglycaemia	2 (0.8%)	0
General disorders and administration site conditions	1 (0.4%)	2 (0.8%)
Asthenia	1 (0.4%)	2 (0.8%)
Fatigue	0	1 (0.4%)
Skin and subcutaneous tissue disorders	0	1 (0.4%)
Urticaria	0	1 (0.4%)
Eye disorders	0	1 (0.4%)
Vision blurred	0	1 (0.4%)
Cardiac disorders	0	2 (0.8%)
Palpitations	0	1 (0.4%)
Congestive cardiomyopathy	0	1 (0.4%)
Vascular disorders	1 (0.4%)	0
Hypertension	1 (0.4%)	0
Investigations	1 (0.4%)	2 (0.8%)
Heart rate increased	0	1 (0.4%)
Gamma-glutamyltransferase increased	0	1 (0.4%)
Heart rate irregular	1 (0.4%)	0
Renal and urinary disorders	0	1 (0.4%)
Dysuria	0	1 (0.4%)
Polyuria	0	1 (0.4%)

Notes: TEAE: Treatment-Emergent Adverse Event
TEAE includes all adverse events (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. 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: 18-May-2009