FDA Briefing Document

NDA 21-888

Zimulti (rimonabant) Tablets, 20 mg

Sanofi Aventis

Advisory Committee – June 13, 2007

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Clinical Review of Safety and Efficacy: Division of Metabolism and Endocrinology Products

Rimonabant Briefing Document

Endocrine and Metabolic Drugs Advisory Committee Meeting

June 13, 2007

NDA 21-888

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ABBREVIATIONS

IND	Investigational New Drug
NDA	New Drug Application
DMEP	Division of Metabolism and Endocrinology Products
BMI	Body Mass Index
RIO	Rimonabant in Obesity
EMEA	European Medical Agency
ECS	Endocannabinoid system
THC	Δ^9-tetrahydrocannabinol
CB_1	Cannabinoid-1
CB_2	Cannabinoid-2
2-AG	2-arachidonoyl glycerol
HPA	Hypothalamic-pituitary-adrenal
CSF	Cerebrospinal fluid
CNS	Central nervous system
CV	Cardiovascular
AUC	Area under the concentration curve
CYP	Cytochrome P450
TC	Total cholesterol
TG	Triglycerides
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
SEM	Standard error of the mean
CI	Confidence interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
DEXA	Dual energy x-ray absorptiometry (bone densitometry)
SOC	System organ class
C_{max}	Maximum concentration
NEC	Not elsewhere classified
PSUR	Periodic safety update report

1. Brief Regulatory History of Rimonabant

An investigational new drug (IND) application for rimonabant was submitted by Sanofi-Aventis to the Division of Metabolism and Endocrinology Products (DMEP) in May 1999.

A New Drug Application (NDA) was submitted to DMEP in April 2005, seeking approval of 20 mg once-daily rimonabant for weight loss, weight maintenance, and prevention of weight regain (hereafter weight management) in patients with a body mass index (BMI) of $\geq$ 30 kg/m^2 or > 27 kg/m^2 when accompanied by at least one risk factor such as hypertension or type 2 diabetes. Sanofi-Aventis also requested approval of rimonabant for the treatment of type 2 diabetes, dyslipidemia, and metabolic syndrome.

The NDA included data from 13,011 subjects/patients from 36 Phase 1 studies, 5 Phase 2 studies (2 studies in weight management, 1 study in smoking cessation, 1 study in the treatment of schizophrenia, and 1 study in the prevention of relapse in alcohol-dependent individuals post detoxification), and 8 Phase 3 studies (4 studies in weight management and 4 studies in smoking cessation).

Four Phase 3 studies were submitted in support of the requested indications. These trials are referred to as Rimonabant in Obesity or RIO North America, RIO Europe, RIO Diabetes, and RIO Lipids. Two doses of rimonabant were examined in the studies, 5 mg and 20 mg once-daily.

Based on the efficacy data from the RIO trials DMEP concluded that rimonabant 20 mg, but not 5 mg, was effective for weight management, but did not believe, for reasons beyond the scope of this document, that the data should be viewed as supporting a specific indication for rimonabant as a primary treatment of type 2 diabetes, dyslipidemia, or the metabolic syndrome.

Moreover, review of the preclinical and clinical data raised concern about associations between rimonabant and increased frequencies of psychiatric adverse events, including suicidality, an ill-defined constellation of neurological signs and symptoms, and seizures. Based on these concerns DMEP sent Sanofi-Aventis an approvable letter in February 2006, requesting that they provide additional data and analyses to more precisely characterize these potential drug-related adverse events.

These additional data and analyses, submitted by Sanofi-Aventis in October 2006, form the basis of this briefing document.

2. World-Wide Regulatory Status of Rimonabant

Rimonabant received marketing approval from the European Medical Agency (EMEA) on June 19, 2006, as an adjunct to diet and exercise for the treatment of obese patients (BMI $\geq$ 30 kg/m^2), or overweight patients (BMI > 27 kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidemia. Rimonabant is currently available in Argentina, Austria, Denmark, Finland, Germany, Ireland, Norway, Sweden, Greece, and the United Kingdom.

3. The Endocannabinoid System

The endocannabinoid system (ECS) was discovered through research into Δ^9-tetrahydrocannabinol (THC), the active ingredient in cannabis. The ECS consists of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes that synthesize and degrade endocannabinoids. There are at least two types of cannabinoid receptor, CB_1 and CB_2. Endogenous agonists for cannabinoid receptors also exist. These "endocannabinoids" are synthesized on demand in response to elevations of intracellular calcium; the two most notable endocannabinoids are N-arachidonoylethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG).
The ECS is found in many regions of the brain including but not limited to: cortex, hippocampus, basal ganglia, cerebellum, striatum, amygdala, and nucleus accumbens; receptor density is particularly high in the cerebellum, cortex, hippocampus, hypothalamus, and basal ganglia. These areas affect memory, motor function, and reward behaviors.

Although CB_1 receptors are expressed by certain non-neuronal cells and tissues, for example, the pituitary gland, immune cells, and reproductive tissues, they are found predominantly at central and peripheral nerve terminals where they mediate inhibition of transmitter release. CB_2 receptors are expressed mainly on immune cells, where they modulate, both within and outside the central nervous system, cytokine release and immune cell migration. Thus, one common role of CB_1 and CB_2 receptors appears to be the regulation of ongoing release of chemical messengers, CB_1 receptors mainly from neurons and CB_2 receptors from immune cells.[1]

As pointed out in a recent review, "endocannabinoids are important modulators in the physiological response of the HPA axis during repetitive stress conditions and in pathological conditions, such as anxiety, phobias, depression, and posttraumatic stress disorders. Moreover, the endocannabinoid system has been proposed as playing an important role in protection against neurotoxicity and, possibly, certain forms of epilepsy. Drugs presumed to increase endocannabinoid tone are therefore currently proposed as a new therapeutic frontier to treat anxiety related disorders and neurodegenerative diseases. The use of drugs acting as antagonists of CB_1 receptors should thus be carefully

1 Pertwee RG. The Therapeutic Potential of Drugs That Target Cannabinoid Receptors or Modulate the Tissue Levels or Actions of Endocannabinoids. *The AAPS Journal.* 2005;7(3):E625-654.

monitored when administered, for instance, to patients with anxiety traits, epilepsy, or neurodegenerative disorders."[2]

There is evidence not only that tissue concentrations of endocannabinoids, cannabinoid receptor density, and/or cannabinoid receptor coupling efficiency increase in a range of different disorders, but also that these increases serve to reduce the severity of signs and symptoms of some of these disorders or even oppose disease progression. Support for the hypothesis that the endocannabinoid system has such an "autoprotective" role has so far come mainly from experiments concerned with pain, multiple sclerosis, cancer, intestinal, mental and cardiovascular disorders, excitotoxicity, traumatic head injury, and Parkinson's disease.[1]

The ECS is believed to play a role in the following:

- Pain. CB_1 receptors are located on pain pathways in the brain and spinal cord and on the central and peripheral terminals of primary afferent neurons that mediate both neuropathic and non-neuropathic pain. Animal studies indicate that the endogenous cannabinoid anandamide and cannabinoid ligands are very effective against chronic pain of both neuropathic and inflammatory origin. Cannabinoid agonists may also release endogenous opioids, and a functional interplay between the endocannabinoid and opioid systems in modulating analgesic responses has been suggested by numerous studies.
- Multiple sclerosis. There is evidence from clinical trials with multiple sclerosis patients that cannabinoids can reduce the spasms, spasticity, or tremor of multiple sclerosis. Furthermore, results from studies using mouse models of multiple sclerosis suggest that cannabinoid CB_1 or CB_2 receptor activation by exogenously administered or endogenously released agonists may oppose the progression of multiple sclerosis by slowing the neurodegenerative process, reducing inflammation, and promoting remyelination.[1]
- Cancer. Numerous studies have suggested that cannabinoids might directly inhibit cancer growth. The proposed mechanisms are complex and may involve induction of apoptosis in tumor cells, anti-proliferative action, and an anti-metastatic effect through inhibition of angiogenesis and tumor cell migration.
- Intestinal disorders. There is evidence that: first, that certain disorders characterized by inflammation of the gastrointestinal tract or by diarrhea may be associated with an increase in intestinal endocannabinoid levels and/or in the expression of CB_1 receptors by mesenteric neurons; second, that the resultant hyperactivity of the endocannabinoid system ameliorates at least some of the symptoms of these diseases; and third, that this amelioration can be mimicked by CB_1 receptor agonists or enhanced by inhibitors of endocannabinoid metabolism.[1]
- Mental disorders. Studies have shown that levels of anandamide are markedly higher in the cerebrospinal fluid of anti-psychotic-naïve first-episode paranoid schizophrenics and of schizophrenics taking "atypical" anti-psychotics than in the

2 Pagotto U, et al. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocrine Reviews.* 2006;27:73-100.

cerebrospinal fluid of healthy controls. CSF anandamide levels are negatively correlated with psychotic symptoms in schizophrenic patients. It is hypothesized that anandamide has a protective role in schizophrenia.

- Excitotoxicity. It has been found that kainic acid elevates anandamide in the hippocampus and that this excitotoxin induces more severe seizures when the CB_1 receptor is genetically deleted or pharmacologically blocked.
- Cardiovascular disorders. CB_1 receptors are much more important than CB_2 receptors in cardiovascular regulation. CB_1 receptors have been detected in the human, rat, and mouse myocardium where they mediate negative inotropy and also in vascular tissues, where their activation leads to vasodilation. Both of these effects appear to be involved in the hypotensive effect of anandamide. Sympathetic nerve terminals contain presynaptic CB_1 receptors, stimulation of which inhibits norepinephrine release, which contributes to the bradycardic effects of anandamide *in vivo*.
- Eye disorders. Endocannabinoids and cannabinoid receptors, in particular CB_1, play an important role in the regulation of intraocular pressure. Endocannabinoids as well as functional CB_1 receptors are present in the retina. Cannabinoids exert neuroprotective effects against retinal neurotoxicity.

4. Pharmacology of Rimonabant

In animal studies, direct CNS administration of endogenous cannabinoids induced a hyperphagic response that was attenuated when the animals were pre-treated with rimonabant.[3] These results suggest a centrally-mediated regulation of appetite; however, effects on CB_1 receptors in the gastrointestinal tract may also modulate satiety as a peripheral means of regulating food intake. Blocking CB_1 receptors located on adipose tissue may improve metabolic derangements often seen in the obese population. In particular, adiponectin, a protein expressed in adipocytes and whose level correlates negatively with insulin resistance, coronary artery disease, and dyslipidemia, may be favorably altered with CB_1 antagonism.

The ECS can exist in a tonically active state from the endogenous release of endocannabinoids onto cannabinoid receptors and also from the presence of CB_1 receptors in a constitutively active state. Rimonabant has been described variably as an antagonist/inverse agonist. The distinction is important in that inverse agonism produces inverse cannabimimetic effects, effects opposite in direction for those produced by cannabinoid receptor agonists. Inverse agonism at receptors is often explained in terms of the two-state model. This proposes that at least some receptor types can exist in two interchangeable conformations, a constitutively active "on" state in which receptors are coupled to their effector mechanisms even in the absence of exogenously added or endogenously produced agonists and a constitutively inactive "off" state that is not spontaneously coupled to receptor effector mechanisms. In terms of this model, agonists increase the proportion of receptors in the "on" state, inverse agonists increase the proportion of receptors in the "off" state and neutral antagonists leave the number of

3 Jamshidi N, Taylor DA. Andamide administration into the ventromedial hypothalamus stimulates appetite in rats. *Br J Pharmacol.* 2001;134:1151-1154.

receptors in each state unaffected. Additionally, there is evidence that the production of inverse cannabimimetic effects by rimonabant does not always depend on the ability of this ligand to displace endogenously released endocannabinoid molecules from CB_1 receptors, and that it can induce inverse cannabimimetic effects at sites that are not located on CB_1 receptors.[4]

5. Pharmacokinetics of Rimonabant

A summary of the pertinent pharmacokinetic features of rimonabant in the obese population are provided below:

- The mean half-life of rimonabant is ~16 days with a maximum of 32 days.
- Single-dose studies in normal weight adults did not show appreciable influence of age or gender on rimonabant's pharmacokinetics.
- The concentration-response relationship was similar between Blacks and Caucasians. Black patients had 75% higher clearance than non-Black patients and consequently the $AUC_{(0-24)}$ was predicted to be 43% lower than in non-Black patients.
- No information was submitted for patients with renal disease; however, this is not thought to be an issue since rimonabant has little renal clearance.
- Mild-to-moderate hepatic impairment had no significant effect on single-dose pharmacokinetics of rimonabant. No dose adjustment is recommended for this population. There are no pharmacokinetic data for patients with severe hepatic impairment.
- Rimonabant is metabolized by both CYP3A and amidohydrolase (predominantly hepatic) pathways *in vitro.* An increase in rimonabant exposure was seen with concomitant administration of ketoconazole (a potent CYP3A4 inhibitor). Other CYP3A4 inhibitors which are likely to increase rimonabant exposure include: itraconazole, ritonavir, telithromycin, clarithromycin, and nefazodone. CYP3A4 inducers which may reduce the concentration of rimonabant include: rifampicin, phenytoin, phenobarbital, carbamazepine, and St. John's wort.
- Rimonabant had a mild inhibitory effect on CYP2C8 *in vitro.*
- No information was submitted for the pediatric population.

6. Rimonabant Clinical Data

As of 18 December 2006, the cumulative database for rimonabant consists of:

- 1308 healthy subjects from 37 completed Phase 1 studies
- 1230 patients from 5 completed Phase 2 studies
- 13,366 patients from 12 completed Phase 3 studies (6483 obese patients in 7 weight management studies and 6883 patients in 5 smoking cessation studies)
- Blinded data from 12,774 subjects/patients from eleven ongoing studies

4 Pertwee RG. Inverse agonism and neutral antagonism at cannabinoid CB_1 receptors. *Life Sciences.* 2005;76:1307-1324.

- Unblinded data from 932 subjects/patients from five studies completed between the October, 2006 re-submission date and the March, 2007 major amendment date.
- Post-marketing data based on approximately 78,610 patients in Europe and Argentina

Table 1: Number of Exposed Subjects from Phase 2 and 3 Studies as of 18 December 2006

PROTOCOL # (PHASE)	TYPE OF PATIENT STUDIED	PLACEBO (N)	RIMONBANT 5 MG (N)	RIMONABANT 20 MG (N)	TREATMENT DURATION (WEEKS)
Previously completed studies:					
DRI 3388 (Phase 2)	Obese patients	73	67	69	16
PDY3796 (Phase 2)	Obese patients	22	-	-	4 (included 23 subjects on 40 mg)
ACT4389 (Phase 2)	Smokers	183	-	-	10
ACT4855 (ACTOL) (Phase 2)	Alcoholic patients	127	-	131	12
METATRIAL (DFI3024,3067,3077,3138) (Phase 2)	Schizophrenic patients	98	-	72	6
EFC4474 (STRATUS EU) (Phase 3)	Smokers	260	256	267	10
EFC4964 (STRATUS US) (Phase 3)	Smokers	261	262	261	10
EFC5794 (STRATUS META) (Phase 3)	Smokers	268	-	262	10
EFC4796 (STRATUS WW) (Phase 3)	Smokers	664 (W11-52)	2016 (W1-10)) 657 (W11-52)	3023 (W1-10) 340 (W11-52)	52
EFC4735 (RIO LIPIDS) (Phase 3)	Overweight & obese dyslipidemics	342	345	346	52
EFC4736 (RIO DIABETES) (Phase 3)	Overweight & obese diabetics	348	358	339	52
EFC4733 (RIO EUROPE) (Phase 3)	Obese patients	305	603	599	104
EFC4743 (RIO NA) (Phase 3)	Obese patients	607 (Y1) 924 (Y2)	1214 (Y1) 300 (Y2)	1219 (Y1) 326 (Y2)	52 Re-randomized for 2nd year
Newly completed studies (since original submission of NDA):					
ACT3801 (CRAVING) (Phase 3)	Obese patients with eating disorder	146	-	143	26

PROTOCOL # (PHASE)	TYPE OF PATIENT STUDIED	PLACEBO (N)	RIMONBANT 5 MG (N)	RIMONABANT 20 MG (N)	TREATMENT DURATION (WEEKS)
EFC5031 (REBA) (Phase 3)	Obese patients	80	-	76	12
EFC5745 (CLAMP) (Phase 3)	Overweight and obese patients with insulin resistance	20	-	20	8
EFC4798 (CIRRUS) (Phase 3)	Smokers	-	-	754	9
Newly completed studies (since resubmission):					
EFC5825 (SERENADE)	Type 2 diabetics	140	-	138	26
DRI5747 Phase 2	Obese Japanese patients	131	133	132	24
Ongoing studies (enrollment extrapolated):					
EFC5823 (ADAGIO lipids)	Abdominally obese with dyslipidemia	401	-	401	52
EFC5827 (STRADIVARIUS)	Overweight with clustering factors	419	-	419	78-86
EFC5828 (AUDITOR)	Abdominally obese/Metabolic syndrome	316	-	316	104-112
EFC5593 (ARPEGGIO)	Type 2 diabetics on insulin	177	-	177	48
EFC5826 (CRESCENDO)	Abdominally obese with 1 other CV RF	3169	-	3168	233
EFC5107 (RAPSODI)	Patients with impaired GTT	1022	-	1022	140
PMC_0172 (VICTORIA)	Increased waist circumference	61	-	61	52
EFC6001 (RIO-Asia)	Overweight & obese Asians	319	-	319	42
RIMON_L_00477 (Phase 4) (CARDIO-REDUSE)	High waist circumference and other cardiometabolic risk factors	34	-	66	-

It is worth highlighting that CRESCENDO, a 50-month cardiovascular outcomes study in 17,000 patients, is scheduled for completion in January 2010.

7. Efficacy of Rimonabant for Weight Management

A. Rimonabant in Obesity – RIO

Rimonabant was developed in accordance with the FDA's 1996 draft Guidance for the Clinical Evaluation of Weight-Control Drugs.[5] As outlined in that document, a weight-loss drug would be considered effective if it satisfied one of the following criteria:

1. The drug's effect is significantly greater than that of placebo with the mean drug-associated weight loss exceeding mean placebo weight loss by at least 5%

2. The proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is significantly greater in subjects on drug than in those on placebo

Four phase 3 clinical studies – RIO Europe, RIO Lipids, RIO Diabetes, and RIO North America - form the basis of the efficacy assessment of rimonabant.

As shown in Table 2, all of these trials were randomized, double-blind, and placebo-controlled and included 20 mg and 5 mg once-daily doses of rimonabant. RIO North America and RIO Europe were two years in duration. RIO Lipids and RIO Diabetes were one-year studies.

Table 2: Rimonabant in Obesity – RIO Trials

STUDY	TREATMENT GROUPS	N	AGE (YEARS)	POPULATION	DURATION	**PRIMARY ENDPOINT/** SECONDARY ENDPOINTS
RIO Europe	Rim 20 mg Y1 (Y2) Rim 5 mg Y1 (Y2) Placebo Y1 (Y2)	599 (355) 603 (363) 305 (168)	18 – 76	Obese patients with or without comorbidities	2 years	**Weight Loss and Weight Maintenance at Year 1** -Weight maintenance at Year 2 -HDL-C & TG -Glucose tolerance
RIO Lipids	Rim 20 mg Rim 5 mg Placebo	346 345 342	20 – 70	Obese patients with untreated dyslipidemia	1 year	**Weight Loss and Weight Maintenance at Year 1** -HDL-C & TG -Glucose tolerance
RIO Diabetes	Rim 20 mg Rim 5 mg Placebo	339 358 348	18 – 70	Obese type 2 diabetics treated with monotherapy	1 year	**Weight Loss and Weight Maintenance at Year 1** -HbA_{1c} -HDL-C & TG
RIO North America	Rim 20 mg Y1 (Y2) Rim 5 mg Y1 (Y2) Placebo Y1 (Y2)	1219 (333) 1214 (300) 607 (924)	18 - 79	Obese patients with or without comorbidities	2 years	**Weight Loss and Weight Maintenance at Year 1** -Prevention of body weight regain during a second year of treatment -HDL-C

B. Primary and Secondary Efficacy Endpoints

5 Draft Guidance for the Clinical Evaluation of Weight-Control Drugs. Issued in September 1996.

The primary efficacy endpoint for the four RIO trials was the absolute change in body weight from baseline to Year 1.

Confirmatory secondary endpoints included:

- Lipid parameters (HDL-C and triglycerides [except RIO North America])
- Glucose tolerance at 1 year (RIO Europe and RIO Lipids)
- Glycemic control parameters (HbA_{1c}) (RIO Diabetes)

Supportive secondary endpoints included:

- Weight loss and weight maintenance at 2 years (RIO Europe and RIO North America)
- Lipid parameters (triglycerides and total cholesterol/HDL-C ratio)
- Glycemic control parameters (fasting glucose and fasting insulin)
- Glucose tolerance at 2 years (RIO Europe)
- Reduction in anti-diabetic medication (RIO Diabetes)

C. Patient Populations

RIO North America and RIO Europe: Patients with a body mass index [BMI] > 27 kg/m^2 with at least 1 co-morbidity or a BMI ≥ 30 kg/m^2 with or without co-morbidities. Diabetic patients were excluded. There were no upper limits for BMI or age.

RIO Lipids: Patients with a BMI > 27 kg/m^2 and untreated dyslipidemia (defined as triglycerides [TG] ≥ 1.69 mmol/L and/or total-cholesterol [TC]/high-density lipoprotein cholesterol [HDL-C] ratio > 4.5 in women or > 5 in men). Patients with overt Type 2 diabetes were excluded.

RIO Diabetes: Patients with a BMI of > 27 kg/m^2 and Type 2 diabetes treated with a single oral anti-diabetic medication, either a sulfonylurea or metformin, who had glycosylated hemoglobin levels (HbA_{1c}) ≥ 6.5% and ≤ 10.0% and fasting glucose levels ≥ 5.55 mmol/L and ≤ 15.04 mmol/L.

Pertinent exclusion criteria:

- Presence of any clinically significant neurological or psychiatric disease;
- History of stroke within 6 months prior to screening visit;
- Presence of treated epilepsy;
- History of severe depression that could be defined as depression necessitating hospitalization, or history of 2 or more recurrent episodes of depression, or history of suicide attempt;
- Presence or recent history (within 6 months prior to screening visit) of Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) substance abuse or dependence;

Excluded medications:

- Prolonged administration (more than 1 week) of anti-depressants (including bupropion) within 3 months prior to screening visit;
- Prolonged administration (more than 1 week) of neuroleptics within 3 months prior to screening visit.

Prohibited medications during the trials:

- Anti-depressants (including bupropion);
- Neuroleptics.

Patients requiring treatment with anti-depressants were to be discontinued from the studies. Sanofi-Aventis explained that this decision was based on concern that some anti-depressants cause weight gain which could interfere with interpretation of the efficacy data.

D. Randomization and Stratification

RIO North America and RIO Europe randomized patients to placebo, rimonabant 5 mg, and rimonabant 20 mg in a 1:2:2 fashion. RIO Diabetes and RIO Lipids randomized patients to placebo, rimonabant 5 mg, and rimonabant 20 mg in a 1:1:1 fashion.

RIO Diabetes was stratified by drug treatment of diabetes: metformin or sulfonylurea, since patients tend to lose weight on metformin and gain weight on sulfonylureas.

RIO Lipids was stratified by triglycerides at screening (≤ 4 g/L, > 4 g/L), since this factor might influence the main secondary endpoints of the study, i.e., the level of HDL-C and TG.

E. Subject Demographics

The majority of the subjects in the RIO studies were middle-aged, Caucasian women (Table 3). Elderly subjects (≥ 65 years) represented 6% of the total study population. More than 1300 subjects had extreme obesity (BMI ≥ 40 kg/m^2). Nearly 70% of the study subjects were from North America and 30% from Europe.

Table 3: Subject Demographics - 1-Year Pooled RIO Data

		PLACEBO N=1602	RIMONABANT	
			5 MG N=2520	20 MG N=2503
Age (years)	Mean (SD)	47.5 (11.4)	46.8 (11.5)	47.2 (11.8)
	Median	48.0	47.0	48.0
	(Min, Max)	(18, 77)	(18, 76)	(18, 79)
Gender	Male	477 (29.8%)	688 (27.3%)	652 (26.0%)
	Female	1125 (70.2%)	1832 (72.7%)	1851 (74.0%)
Race	Caucasian	1443 (90.1%)	2227 (88.4%)	2218 (88.6%)
	Black	96 (6.0%)	187 (7.4%)	192 (7.7%)
	Asian	8 (0.5%)	12 (0.5%)	17 (0.7%)
	Other	55 (3.4%)	94 (3.7%)	76 (3.0%)
Geographical area	North America	1050 (65.5%)	1710 (67.9%)	1715 (68.5%)
	Europe	498 (31.1%)	758 (30.1%)	729 (29.1%)
	Other countries	54 (3.4%)	52 (2.1%)	59 (2.4%)

F. Subject Disposition

The withdrawal rates during the first year of the four RIO studies ranged from 34%-47% (Table 4). The largest percentage of drop-outs occurred in RIO North America and the lowest in RIO-Diabetes.

Table 4: Subject Disposition – 1-Year Pooled RIO Data

DISPOSITION OF PATIENTS	PLACEBO N=1602 N (%)	RIMONABANT	
		5 MG N=2220 N (%)	20 MG N=2176 N (%)
Completed study treatment period	785 (49.0)	931 (41.9)	973 (44.7)
Study treatment discontinuation	817 (51.0)	1289 (58.1)	1203 (55.3)
Main reason for treatment discontinuation:			
Disease progression/lack of efficacy	52 (3.2)	77 (3.5)	51 (2.3)
Recovery	0	0	2 (<0.1)
Adverse event	265 (16.5)	475 (21.4)	574 (26.4)
Poor compliance to protocol	57 (3.6)	103 (4.6)	73 (3.4)
Investigator/subject's request	341 (21.3)	508 (22.9)	391 (18.0)
Subject lost to follow-up	78 (4.9)	80 (3.6)	83 (3.8)
Other reason	22 (1.4)	34 (1.5)	27 (1.3)

As of 18 December 2006, 441 patients had been exposed to 20 mg once-daily rimonabant for two years.

G. Weight-Loss Efficacy at One Year

Unless otherwise indicated, all efficacy analyses use last-observation-carried-forward data.

The mean placebo-subtracted weight loss for the rimonabant 20 mg treatment groups ranged from -3.9 kg to -5.4 kg (Tables 5 and 6). Forty-nine to 58% of the subjects treated with rimonabant 20 mg lost at least 5% of baseline body weight compared with 15% to 20% of subjects treated with placebo. Weight loss with rimonabant 5 mg was much less than with rimonabant 20 mg.

Table 5: Change in Body Weight from Baseline to Year 1 – RIO N.A. and Europe

EFFICACY DATA	RIO NORTH AMERICA			RIO EUROPE		
	PLACEBO N=607	**5 MG N=1214**	**20 MG N=1219**	**PLACEBO N=305**	**5 MG N=603**	**20 MG N=599**
Mean Change (kg) Range	-1.6 -38.7 to 14.6	-2.9** -93.1 to 15.0	-6.3** -46.3 to 26.2	-1.8 -39.0 to 17.0	-3.4* -38.7 to 18.3	-6.6** -42.1 to 14.1
Mean % Change Range	-1.6 -27.4 to 10.1	-2.8 -50.3 to 12.1	-6.2 -40.4 to 26.3	-1.8 -31.0 to 16.6	-3.4 -31.2 to 20.5	-6.6 -39.7 to 13.4
5% Responders N (%)	11.8 (20.0)	31.1 (26.1)	57.8 (48.6)	58 (19.2)	19.8 (33.2)	30.3 (50.9)
10% Responders N (%)	50 (8.5)	12.6 (10.6)	30.0 (25.2)	22 (7.3)	60 (10.1)	16.3 (27.4)

*p<0.05; **p<0.001 for mean difference to placebo. Conversion equation: kg x 2.2 = pounds

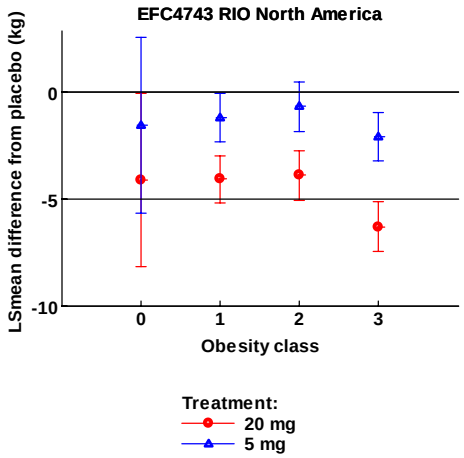
Table 6: Change in Body Weight from Baseline to Year 1 – RIO Lipids and Diabetes

EFFICACY DATA	RIO LIPIDS			RIO DIABETES		
	PLACEBO N=342	**5 MG N=345**	**20 MG N=346**	**PLACEBO N=348**	**5 MG N=358**	**20 MG N=339**
Mean Change (kg) Range	-1.5 -21.9 to 10.4	-3.1** -20.3 to 13.4	-6.9** -27.7 to 6.0	-1.4 -18.5 to 6.8	-2.3* -24.5 to 7.7	-5.3** -34.7 to 9.1
Mean % Change Range	-1.6 -22.1 to 11.9	-3.4 -22.3 to 15.2	-7.5 -24.4 to 7.7	-1.5 -18.1 to 8.1	-2.4 -22.1 to 6.2	-5.6 -35.7 to 10.0
5% Responders N (%)	65 (19.5)	102 (30.0)	201 (58.4)	50 (14.5)	77 (21.7)	166 (49.4)
10% Responders N (%)	24 (7.2)	36 (10.6)	112 (32.6)	7 (2.0)	22 (6.2)	55 (16.4)

*p<0.05; **p<0.001 for mean difference to placebo. Conversion equation: kg x 2.2 = pounds.

The weight loss effect in all of the RIO studies, except RIO Europe, was driven in large part by individuals who were in the baseline category of extreme obesity (BMI $\geq$ 40 kg/m^2). This is graphically illustrated below for the RIO-North America study. The classes of obesity are defined as: 0, <30 kg/m^2; 1, 30-34.9 kg/m^2; 2, 35-39.9 kg/m^2; and 3, $\geq$ 40 kg/m^2.

Figure 1: Weight Loss Effect by BMI Category



The change in BMI from baseline to Year 1 for the 4 RIO studies is presented in Table 7.

Table 7: Change in BMI from Baseline to Year 1

	RIO LIPIDS			RIO DIABETES		
	Placebo N=342	**5 mg N=345**	**20 mg N=346**	**Placebo N=348**	**5 mg N=358**	**20 mg N=339**
Mean change in BMI (SD)	-0.5 (1.8)	-1.1 (1.7)	-2.5 (2.2)	-0.5 (1.2)	-0.8 (1.4)	-1.9 (1.8)
	RIO-NORTH AMERICA			**RIO EUROPE**		
	Placebo N=607	**5 mg N=1214**	**20 mg N=1219**	**Placebo N=305**	**5 mg N=603**	**20 mg N=599**
Mean change in BMI (SD)	-0.6 (2.0)	-1.0 (2.2)	-2.3 (2.6)	-0.7 (2.3)	-1.2 (2.1)	-2.4 (2.6)

H. Weight-Loss Efficacy at Two Years

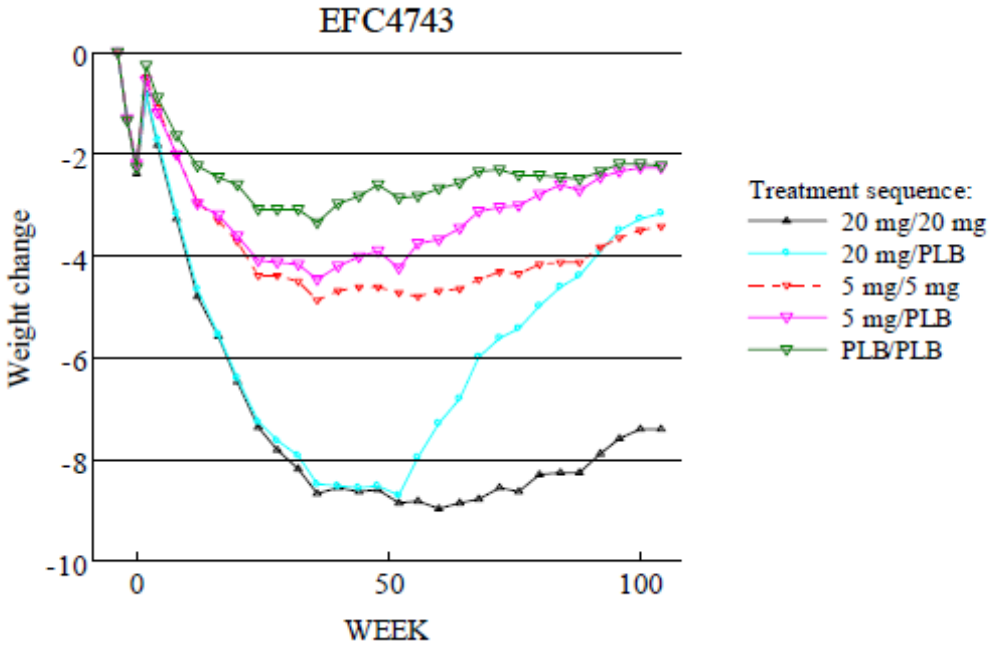
To demonstrate persistence or maintenance of weight loss, subjects in RIO North America who were initially randomized to placebo remained on placebo for a second year and subjects initially randomized to rimonabant were re-randomized after the first year to continue on rimonabant or placebo during the second year.

Table 8 and Figure 2 below display descriptive statistics for weight regain for the 5 treatment groups. The weight regain mean difference was -0.8 kg (p=0.1) between the 5 mg/5 mg group and the 5 mg/placebo group and -4.1 kg (p < 0.0l) between the 20 mg/20 mg group and the 20 mg/placebo group.

Table 8: Descriptive Statistics for Weight Regain

		Plb/Plb		5 mg/Plb		5 mg/5 mg		20 mg/Plb		20 mg/20 mg
LOCF	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	292	103.2 (21.9)	294	105.7 (21.4)	296	104.1 (20.8)	323	102.8 (19.9)	328	102.1 (20.7)
Year 1 (RRB)	292	100.2 (22.8)	294	101.3 (22.1)	296	99.3 (21.4)	323	94.1 (20.0)	328	93.2 (20.8)
Year 2 weight	292	100.9 (23.2)	294	103.4 (22.9)	296	100.6 (22.6)	323	99.6 (20.9)	328	94.6 (20.9)
Change (RRB) (regain)	292	0.6 (5.0)	294	2.0 (5.3)	296	1.4 (5.6)	323	5.6 (5.3)	328	1.4 (5.0)
Percent change (RRB)	292	0.7 (5.0)	294	2.1 (5.3)	296	1.3 (5.6)	323	6.2 (5.9)	328	1.7 (5.1)

Figure 2: Mean Weight Change from Baseline to Year 2 – RIO North America



In RIO Europe patients remained on the same treatment throughout the two-year study. At the end of the study the mean placebo-subtracted weight loss for the rimonabant 20 mg group was -4.3 kg, and -1.7 kg for the rimonabant 5 mg group.

I. Secondary efficacy variables

The efficacy results for the pre-specified confirmatory secondary endpoints in each of the RIO studies are presented in Table 9.

Table 9: Secondary Efficacy Results

EFFICACY PARAMETER	PLACEBO	RIMONABANT 5 MG	RIMONABANT 20 MG
RIO-North America			
HDL			
Mean % change	5.4 (15.4)	7.6 (15.4)	12.6 (17.2)
Mean difference (SEM)		2.3 (0.9)	7.2 (0.9)
p-value		0.008	<0.001

EFFICACY PARAMETER	PLACEBO	RIMONABANT 5 MG	RIMONABANT 20 MG
RIO-Europe			
HDL			
Mean % change	13.4 (18.3)	16.2 (18.7)	22.3 (20.7)
Mean difference (SEM)		2.8 (1.4)	8.9 (1.4)
p-value		0.048	<0.001
Triglycerides			
Mean % change	8.3 (43.0)	5.7 (44.5)	-6.8 (34.4)
Mean difference (SEM)		-2.6 (3.0)	-15.1 (3.0)
p-value		0.377	<0.001
Oral GTT			
Improvement (%)	19 (70.4)	40 (62.5)	38 (66.7)
No improvement (%)	8 (29.6)	24 (37.5)	19 (33.3)
p vs. placebo		0.473	0.734
RIO-Lipids			
HDL			
Mean % change	11.0 (15.8)	14.2 (17.6)	19.1 (20.9)
Mean difference (SEM)		3.3 (1.5)	8.1 (1.5)
p-value		0.025	<0.001
Triglycerides			
Mean % change	-0.2 (38.7)	1.2 (39.4)	-12.6 (41.2)
Mean difference (SEM)		1.3 (3.2)	-12.4 (3.2)
p-value		0.677	<0.001
Oral GTT			
Improvement	32 (55.2)	33 (50.0)	38 (66.7)
No improvement	26 (44.8)	33 (50.0)	19 (33.3)
p vs. placebo		0.565	0.207
RIO-Diabetes			
HbA_{1c}			
Mean % change	0.1 (1.0)	-0.1 (1.0)	-0.6 (0.8)
Mean difference (SEM)		-0.2 (0.1)	-0.7 (0.1)
p-value		0.076	<0.001
HDL			
Mean % change	7.1 (13.5)	9.2 (15.8)	15.4 (17.4)
Mean difference (SEM)		2.2 (1.2)	8.4 (1.2)
p-value		0.076	<0.001
Triglycerides			
Mean % change	7.3 (43.0)	1.3 (35.1)	-9.1 (44.3)
Mean difference (SEM)		-5.9 (3.2)	-16.4 (3.3)
p-value		0.066	<0.001

Supportive secondary efficacy variables included fasting glucose and fasting insulin levels, and reduction in anti-diabetic medication. The results of these endpoints are summarized in Tables 10 and 11 below.

Table 10: Supportive Secondary Efficacy Variables

EFFICACY DATA	RIO-LIPIDS			RIO-DIABETES		
	Placebo N=342	**5 mg N=345**	**20 mg N=346**	**Placebo N=348**	**5 mg N=358**	**20 mg N=339**
Mean change in fasting glucose mmol/L (SD)	-0.05 (0.62)	-0.01 (0.62)	-0.08 (0.58)	0.33 (2.32)	0.30 (2.06)	-0.64 (1.96)**
Mean change in fasting insulin uIU/ml (SD)	0.9 (15.9)	0.4 (10.3)	-1.7 (12.4)*	0.4 (14.8)	0.7 (9.0)	-0.7 (9.9)
EFFICACY DATA	**RIO-NORTH AMERICA**			**RIO-EUROPE**		
	Placebo N=607	**5 mg N=1214**	**20 mg N=1219**	**Placebo N=305**	**5 mg N=603**	**20 mg N=599**
Mean change in fasting glucose mmol/L (SD)	0.06 (0.58)	0.04 (0.57)	0.02 (0.68)	0.03 (0.77)	-0.05 (0.68)	-0.09 (0.65)*
Mean change in fasting insulin µIU/ml (SD)	2.6 (16.7)	0.9 (12.3)*	-0.2 (10.5)**	1.8 (13.0)	0.3 (11.2)	-1.0 (8.8)**

*p<0.05, **p<0.001 for mean change compared to placebo. Conversion equation: mmol/L x 18 = mg/dL

Table 11: Changes in Anti-Diabetic Medication - RIO Diabetes

CHANGES IN ANTI-DIABETIC TREATMENT	PLACEBO N=345 N (%)	RIMONABANT 5 MG N=358 N (%)	RIMONABANT 20 MG N=339 N (%)
No change	268 (77.7)	279 (78.6)	255 (75.9)
Upward adjustment	44 (12.8)	49 (13.8)	38 (11.3)
Downward adjustment	26 (7.5)	22 (6.2)	40 (11.9)
Another drug due to insufficient efficacy	7 (2.0)	3 (0.8)	0
Another drug due to other reasons	0	2 (0.6)	3 (0.9)

In general, there were small improvements in systolic and diastolic blood pressure in patients treated with rimonabant 20 mg compared with placebo (Table 12).

Table 12: Changes in Blood Pressure

PARAMETER	RIO-NORTH AMERICA		RIO-EUROPE		RIO-LIPIDS		RIO-DIABETES	
	PLACEBO	20 MG	PLACEBO	20 MG	PLACEBO	20 MG	PLACEBO	20 MG
SBP (mm Hg)								
N	590	1191	301	595	334	344	345	336
Baseline mean (SD)	121.7 (12.3)	121.8 (12.7)	126.8 (13.7)	127.0 (14.1)	124.0 (13.8)	124.9 (12.7)	128.7 (13.1)	130.3 (12.6)
Mean change (SD)	-0.1 (12.0)	-0.3 (12.2)	0.3 (12.3)	-1.0 (12.5)	-0.3 (10.1)	-2.1 (12.3)	1.6 (13.2)	-0.8 (12.8)
LS mean difference (SEM) [95% CI]		-0.2 (0.6) [-1.4, 1.0]		-1.2 (0.9) [-3.0, 0.5]		-1.7 (0.9) [-3.5, -0.0]		-2.3 (1.0) [-4.3, -0.4]
p vs placebo		0.750		0.161		0.048		0.020
DBP (mm Hg)								
N	590	1191	301	595	334	344	345	336
Baseline mean (SD)	78.1 (7.8)	77.7 (8.2)	79.7 (8.5)	79.4 (8.8)	78.2 (8.4)	78.2 (7.7)	78.8 (7.8)	79.0 (7.8)
Mean change (SD)	-0.4 (8.3)	-0.2 (8.2)	0.1 (8.5)	-0.9 (8.7)	-0.2 (7.4)	-1.7 (8.5)	-0.7 (8.4)	-1.9 (8.2)
LS mean difference (SEM) [95% CI]		0.2 (0.4) [-0.6, 1.0]		-1.0 (0.6) [-2.2, 0.2]		-1.6 (0.6) [-2.8, -0.4]		-1.2 (0.6) [-2.5, 0.0]
p vs placebo		0.655		0.096		0.011		0.060

In RIO Lipids, although there were no significant differences between the rimonabant 20 mg and placebo groups in the changes in TC or LDL-C, there were statistically significant decreases in the ratio of TC/HDL-C in the rimonabant 20 mg vs. the placebo group.

J. Body Composition

Body composition was measured with body DEXA in a subset of patients in RIO Lipids. Decreases in the rimonabant 20 mg group relative to placebo were observed in the total body mass ($p<0.001$), the total body fat mass ($p=0.001$) and the fat mass/total body mass ratio ($p=0.007$). There was no statistically significant difference between the 20 mg and the placebo groups in lean mass loss between groups. No difference between the rimonabant 5 mg group and the placebo groups was observed in any of the total body composition parameters.

8. Efficacy Conclusions

Rimonabant 20 mg daily vs. placebo was associated with statistically and clinically significant weight loss. Rimonabant 5 mg daily vs. placebo was associated with statistically significant but clinically insignificant weight loss.

In RIO Lipids, rimonabant 20 mg daily vs. placebo was associated with a statistically significant 8% increase in HDL-C and a statistically significant 12% decrease in TG levels. There were no significant improvements in levels of total or LDL-C in the rimonabant 20 mg daily vs. placebo group.

In RIO Diabetes, rimonabant 20 mg compared with placebo was associated with a statistically significant 0.7% reduction in HbA_{1c} in overweight and obese subjects with type 2 diabetes taking either metformin or a sulfonylurea.

In general, there were small improvements in systolic and diastolic blood pressure in subjects treated with rimonabant 20 mg daily compared with placebo.

9. SAFETY ISSUES

When considering the results of the following analyses of safety data, it should be borne in mind that the p-values and confidence intervals for all between-group comparisons are nominal; that is, no adjustments have been made for multiple evaluations.

A. Psychiatric Adverse Events

As mentioned previously, endocannabinoids are important modulators in pathological conditions such as anxiety, phobias, depression, and posttraumatic stress disorders. Therefore, the emergence of psychiatric symptoms with the use of a cannabinoid receptor antagonist/inverse agonist is biologically plausible.

Among the most significant adverse events throughout the Phase 3 program were those in the primary System Organ Class (SOC) Psychiatric Disorders, specifically depressive events, anxiety, psychomotor agitation, and sleep disorders. In the pooled RIO studies, for subjects receiving the same treatment during the whole study, 26% of rimonabant 20-mg treated subjects vs. 14% of placebo treated subjects experienced a psychiatric symptom reported as an adverse event. Specifically, 9% of rimonabant 20-mg treated subjects vs. 5% of placebo treated subjects reported symptoms of depression (depressed mood; depression; depressive symptom; or major depression).

Tabulated below are the psychiatric symptoms (by Preferred Term) reported as adverse events from the pooled RIO studies for those subjects who received the same treatment during the entire study. For convenience, preferred terms have been ordered in decreasing frequency based on occurrence at the 20 mg dose.

Table 13: Psychiatric Symptoms Reported as Adverse Events - Pooled RIO Studies

ADVERSE EVENT PREFERRED TERM	PLACEBO N=1602 (%)	5 MG N=2220 (%)	20 MG N=2176 (%)
Total # of patients reporting symptom	**226 (14.1)**	**356 (16.0)**	**569 (26.2)**
Anxiety	40(2.50)	68 (3.06)	131 (6.02)
Insomnia	53 (3.31)	66 (2.97)	118 (5.42)
Depressed mood	45 (2.81)	66 (2.97)	83 (3.81)
Depression	23 (1.44)	55 (2.48)	74 (3.40)
Stress	28 (1.75)	35(1.58)	38 (1.75)
Nervousness	5 (0.31)	14 (0.63)	31 (1.42)
Depressive symptom	12 (0.75)	15 (0.68)	23 (1.06)
Sleep disorder	7 (0.44)	13 (0.59)	21 (0.97)
Nightmare	3 (0.19)	4 (0.18)	21 (0.97)
Panic attack	1 (0.06)	3 (0.14)	18 (0.83)
Mood altered	4 (0.25)	5 (0.23)	15 (0.69)
Major depression	5 (0.31)	5 (0.23)	15 (0.69)
Mood swings	2 (0.12)	11 (0.50)	10 (0.46)
Agitation	2 (0.12)	5 (0.23)	10 (0.46)
Affect lability	1 (0.06)	7 (0.32)	10 (0.46)
Aggression	1 (0.06)	6 (0.27)	9 (0.41)
Abnormal dreams	2 (0.12)	1 (0.045)	8 (0.37)
Affective disorder	3 (0.19)	1 (0.04)	7 (0.32)
Decreased libido	6 (0.37)	4 (0.18)	6 (0.28)
Anger	1 (0.06)	2 (0.09)	6 (0.28)
Sleep walking	0	1 (0.045)	5 (0.23)
Restlessness	2 (0.12)	1 (0.04)	5 (0.23)
Hallucination, visual	0	0	5 (0.23)
Emotional disorder	1 (0.06)	1 (0.04)	5 (0.23)
Burnout syndrome	2 (0.12)	7 (0.32)	5 (0.23)
Loss of libido	0	1 (0.04)	4 (0.18)
Disorientation	0	1 (0.04)	4 (0.18)
Crying	1 (0.06)	1 (0.04)	4 (0.18)
Apathy	0	2 (0.09)	4 (0.18)
Mental disorder	1 (0.06)	0	3 (0.14)
Dysthymic disorder	1 (0.06)	6 (0.27)	3 (0.14)
Confusional state	0	1 (0.04)	3 (0.14)
Adjustment disorder with mixed anxiety and depressed mood	0	1 (0.04)	3 (0.14)
Adjustment disorder with depressed mood	0	1 (0.045)	3 (0.14)
Adjustment disorder	1 (0.06)	1 (0.04)	3 (0.14)
Initial insomnia	2 (0.12)	2 (0.09)	3 (0.14)
Middle insomnia	2 (0.12)	5 (0.23)	3 (0.14)
Tearfulness	0	0	2 (0.09)
Personality disorder	2 (0.12)	0	2 (0.09)
Hallucination, auditory	0	0	2 (0.09)
Generalized anxiety disorder	1 (0.06)	0	2 (0.09)
Dissociation	0	0	2 (0.09)

ADVERSE EVENT PREFERRED TERM	PLACEBO N=1602 (%)	5 MG N=2220 (%)	20 MG N=2176 (%)
Bulemia	0	0	2 (0.09)
Bereavement reaction	1 (0.06)	3 (0.14)	2 (0.09)
Anhedonia	1 (0.06)	0	2 (0.09)
Thought blocking	0	0	1 (0.05)
Tension	0	1 (0.04)	1 (0.05)
Seasonal affective disorder	0	0	1 (0.05)
Premature ejaculation	0	0	1 (0.05)
Panic disorder	0	1 (0.04)	1 (0.05)
Ochlophobia	0	0	1 (0.05)
Noctiphobia	0	0	1 (0.05)
Mania	0	0	1 (0.05)
Libido increased	0	0	1 (0.05)
Flashback	0	0	1 (0.05)
Fear	0	0	1 (0.05)
Emotional distress	0	2 (0.09)	1 (0.05)
Dysphoria	0	0	1 (0.05)
Dysphemia	0	1 (0.045)	1 (0.05)
Depersonalization	0	0	1 (0.05)
Delusional disorder	0	0	1 (0.05)
Daydreaming	0	0	1 (0.05)
Claustrophobia	0	0	1 (0.05)
Bipolar disorder	1 (0.06)	0	1 (0.05)
Anxiety disorder	0	1 (0.045)	1 (0.05)
Parasomnia	0	0	1 (0.05)
Sleep terror	0	1 (0.045)	1 (0.05)
Early morning awakening	1 (0.12)	0	1 (0.05)

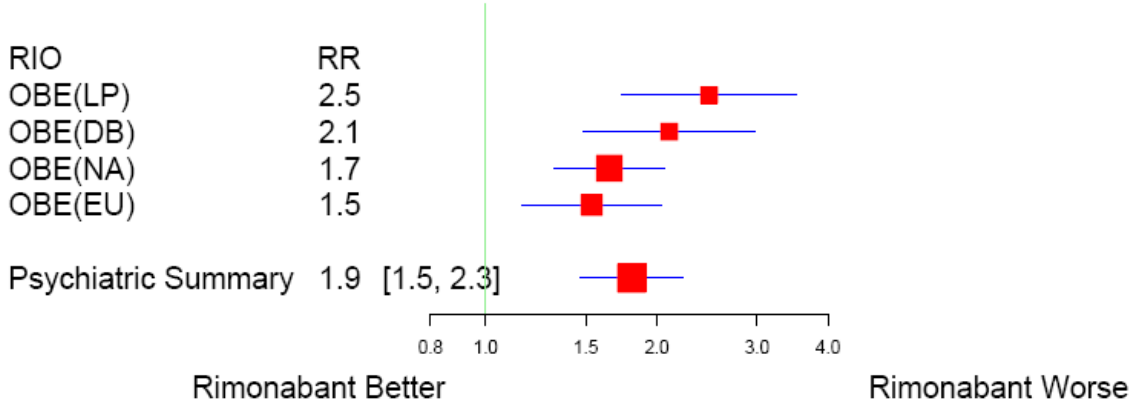
Subjects receiving the same treatment during the whole study

It is worth highlighting that the preferred term "irritability" was a relatively common adverse event, but was placed in a different primary system organ class, and therefore did not appear among the psychiatric adverse events. The occurrence of "irritability" was greater in the rimonabant 20 mg group than in the rimonabant 5 mg or placebo groups: 1.93%, 1.35%, and 0.56%, respectively.

A retrospective analysis of source documentation was performed by Sanofi-Aventis in order to obtain additional data on specific psychiatric events. Attempts were made to capture associated psychiatric symptoms, most notably psychomotor agitation, psychomotor retardation, anxiety, suicidal ideation, aggressivity, irritability, etc. An individual could report multiple symptoms; these symptoms were not recorded on an adverse event report form and are therefore over and above the total number of adverse events noted above. These included 155 additional symptoms associated with depressed mood disorders and 208 additional symptoms of anxiety disorders in subjects receiving rimonabant 20 mg vs. 49 and 51, respectively in the placebo group. Overall, the number of associated symptoms reported by subjects reporting a psychiatric adverse event was 427 in the rimonabant 20-mg treated group and 118 in the placebo-treated group.

As shown in Figure 3, the relative risk for psychiatric adverse events in the rimonabant 20 mg vs. placebo groups ranged from 1.5 to 2.5 in the four RIO studies. When considered in aggregate, the overall relative risk for psychiatric adverse events in the rimonabant 20 mg vs. placebo group was 1.9 (1.5, 2.3).

Figure 3: Relative Risk of Psychiatric Adverse Event - Rimonabant 20 mg vs. Placebo - RIO studies



Kaplan-Meier curves of the time to first treatment-emergent psychiatric adverse event can be found in the Appendix. These analyses indicate a clear and early separation of the curves for rimonabant 20-mg treated subjects and placebo treated subjects. These psychiatric adverse events more often necessitated discontinuation of study drug; more often required concomitant treatment (pharmacologic and/or psychotherapy); and were more often reported as "Not Recovered" or "Recovering" at end of study, in the rimonabant 20-mg treated group vs. the placebo-treated group.

The number of subjects requiring the institution of an anxiolytic or hypnotic agent for a psychiatric adverse event was: 185 subjects (8.5%) on rimonabant 20 mg vs. 102 subjects (4.6%) on rimonabant 5 mg, and 66 subjects (4.1%) on placebo. Another 104 subjects (4.8%) on rimonabant 20 mg vs. 88 subjects (4.0%) on rimonabant 5 mg and 46 subjects (2.9%) on placebo required the institution of an anti-depressant agent for a psychiatric adverse event.

Suicidality

To investigate a signal for suicidality detected during review of the original NDA submission, DMEP requested that Sanofi-Aventis obtain a formal assessment of suicidality from Dr. Kelly Posner's group at Columbia University. Dr. Posner and her colleagues have been integrally involved in the recent assessment by FDA of suicidality in patients taking anti-depressant drugs.

The Columbia University group's method of assessment is based on a blinded classification of cases according to the following categories of interest:

Category

1 Completed suicide
2 Suicide attempt (*Self-injurious behavior associated with some intent to die. Intent can be stated or inferred by rater.)*
3 Preparatory acts toward imminent suicide behavior *(Person takes steps to injure self but is stopped by self or other. Intent to die is either stated or inferred.)*
4 Suicidal ideation *(Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior.)*
5 Self-injurious behavior, intent unknown *(Self-injurious behavior where associated intent to die is unknown and cannot be inferred.)*
6 Not enough information (fatal) *(Insufficient information to classify the event.)*
9 Not enough information (non-fatal) *(Insufficient information to classify the event.)*

Sanofi-Aventis searched the original clinical adverse event database to identify patients for whom additional information was needed. For these events, efforts were made to better document the case, either from source documents already collected during the course of the studies, or collected after returning to the sites. Patient narratives were then prepared or updated and submitted to Dr. Posner's group.

A total of 1201 patient-narratives were assessed in a strictly blinded manner by the Columbia University group. Ninety-one (91) cases were classified as either possibly (Columbia categories 5, 6, or 9), or definitely (Columbia categories 1, 2, 3, or 4) suicidal; this includes 5 cases which occurred on haloperidol active treatment.

The tables below summarize all possible and/or definite cases of suicidality as adjudicated by the Columbia University group for all completed studies as of 18 December 2006. A total of 13 studies were used in the analyses: Study ACT4389 (which had no 20 mg rimonabant treatment group) and study EFC4798 (which had no placebo treatment group) and study DRI5747 (which did not have a clinical study report completed as of the cut-off date) were excluded from the analyses. Studies EFC4743 and EFC4796 re-randomized patients during a maintenance phase treatment after the first randomized treatment. Only data from the first randomization were used in the analyses. Thus, the total number of suicidality cases contributing to the analyses is 74 (20 on placebo, 8 on rimonabant 5 mg, and 46 on rimonabant 20 mg).

Table 14: Columbia Classification of Suicidality Events

C-CASA Classification	Placebo (n=2909)	5 mg (n=5121)	20 mg (n=6802)
1 Complete suicide			
2 Suicide attempt	7		4
3 Preparatory acts toward imminent suicide		1	
4 Suicidal ideation	13	6	39
5 Self-injurious behavior, intent unknown			
6 Not enough information (fatal)		1	
9 Not enough information (non-fatal)			3

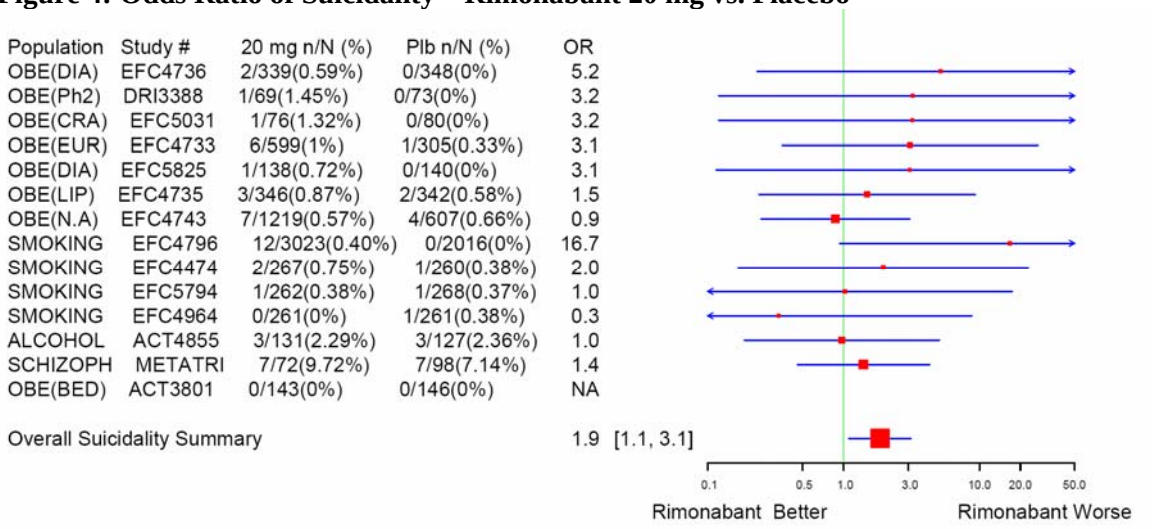
Table 15: Possible and/or Definite Cases of Suicidality – First Randomization

STUDY #	POPULATION	PLACEBO INCIDENCE (%) AND INCIDENT RATE (/100 PERSON-YEARS)	RIM 5 MG INCIDENCE (%) AND INCIDENT RATE (/100 PERSON-YEARS)	RIM 20 MG INCIDENCE (%) AND INCIDENT RATE (/100 PERSON-YEARS)
ACT4855	Alcoholics	3/127 (2.36) 3/23.5 (12.77)		3/131 (2.29) 3/26.2 (11.45)
METATRIAL	Schizophrenics	7/98 (7.14) 7/5.6 (125)		7/72 (9.72) 7/4.0 (175)
EFC4474	Smokers	1/260 (0.38) 1/41.1 (2.43)	1/256 (0.39) 1/39.6 (2.53)	2/267 (0.75) 2/41.5 (4.82)
EFC4964	Smokers	1/261 (0.38) 1/42.9 (2.33)	1/262 (0.38) 1/42.3 (2.36)	0/261 0/43.0
EFC5794	Smokers	1/268 (0.37) 1/43.8 (2.28)		1/262 (0.38) 1/42.0 (2.38)
EFC4796	Smokers	0/664 0/366.3	0/2016 0/311.2	12/3023 (0.40) 12/460.1 (2.61)
DRI3388	Obese	0/73 0/16.5	0/67 0/17.1	1/69 (1.45) 1/18.6 (5.38)
EFC4733	Obese	1/305 (0.33) 1/377.8 (0.26)	0/603 0/794.5	6/599 (1.00) 6/761.8 (0.79)
EFC4735	Obese	2/342 (0.58) 2/268.2 (0.75)	2/345 (0.58) 2/262.3 (0.76)	3/346 (0.87) 3/266.8 (1.12)
EFC4736	Obese	0/348 0/277.7	0/358 0/283.6	2/339 (0.59) 2/269.4 (0.74)

STUDY #	POPULATION	PLACEBO INCIDENCE (%) AND INCIDENT RATE (/100 PERSON-YEARS)	RIM 5 MG INCIDENCE (%) AND INCIDENT RATE (/100 PERSON-YEARS)	RIM 20 MG INCIDENCE (%) AND INCIDENT RATE (/100 PERSON-YEARS)
EFC4743	Obese	4/607 (0.66) 4/415.1 (0.96)	4/1214 (0.33) 4/837.1 (0.48)	7/1219 (0.57) 7/867.4 (0.81)
EFC5031	Obese	0/80 0/18.1		1/76 (1.32) 1/16.5 (6.06)
EFC5825	Obese	0/140 0/63.9		1/138 (0.72) 1/59.6 (1.68)

The overall odds ratio (CI) for the incidence of suicidality: 20 mg versus placebo for the cases indicated above was 1.9 (1.1, 3.1) (Figure 4).

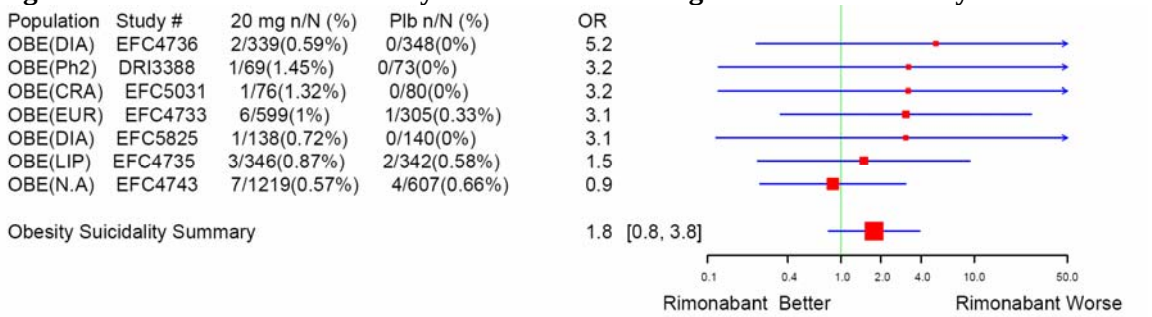
Figure 4: Odds Ratio of Suicidality – Rimonabant 20 mg vs. Placebo



EFC4796: Rimonabant 20 mg compared to active comparator (5 mg) for analysis as there was no placebo arm in first randomization.

When limited to the 7 obesity studies, the odds ratio for incidence of suicidality: 20 mg versus placebo was 1.8 (0.8, 3.8) (Figure 5).

Figure 5: Odds Ratio of Suicidality – Rimonabant 20 mg vs. Placebo - Obesity Studies



The 74 cases of suicidality were analyzed with respect to age, gender, time-to-event, BMI and country. The table below provides a summary of these observations.

Table 16: Demographics for Suicidality Cases

	PLACEBO N=20	RIMONABANT 5 MG N=8	RIMONABANT 20 MG N=46
All Indications			
Age (in years)			
Mean	43.2	41.6	42.9
Range	22, 61	27, 63	21, 64
Gender			
Males (%)	13 (65)	4 (50)	16 (34.8)
Females (%)	7 (35)	4 (50)	30 (65.2)
BMI (kg/m^2)			
Mean	32.2	33.3	32
Range	19.9, 63.8	22.1, 39.2	19.1, 63.3
Country			
U.S. (%)	15 (75)	6 (75)	26 (56.5)
Europe (incl UK) (%)	4 (20)	1 (12.5)	13 (28.3)
Canada (%)	1 (5)	1 (12.5)	6 (13)
Australia (%)	0	0	1 (2.2)
Time-to-event (in days)			
Mean	63.6	82.9	98.7
Median	33	74	44.5
Min, max	1, 225	13, 157	1, 610
Obesity Indication			
	PLACEBO **N=7**	**RIMONABANT 5 MG** **N=6**	**RIMONABANT 20 MG** **N=21**
Age (in years)			
Mean	41.7	43.5	46.1
Range	22, 54	29, 63	27, 60
Gender			
Males (%)	3 (42.9)	4 (66.7)	2 (9.5)
Females (%)	4 (57.1)	2 (33.3)	19 (90.5)
BMI (kg/m^2)			
Mean	45.3	36.1	36.5
Range	30.3, 63.8	31.5, 39.2	29.4, 54.2
Country			
U.S. (%)	6 (85.7)	5 (83.3)	8 (38.1)
Europe (incl UK) (%)	0	0	8 (38.1)
Canada (%)	1 (14.3)	1 (16.7)	5 (23.8)
Australia (%)	0	0	0
Time-to-event (in days)			
Mean	117	82.9	181.6
Median	120	101	142
Min, max	1, 225	58, 157	14, 610
U.S. Subjects/Obese only			
	PLACEBO **N=6**	**RIMONABANT 5 MG** **N=5**	**RIMONABANT 20 MG** **N=8**
Age (in years)			
Mean	39.7	44.2	45.6
Range	22, 50	29, 63	27, 60
Gender			

Males (%) Females (%)	3 (50) 3 (50)	3 (60) 2 (40)	0 8 (100)
BMI (kg/m^2) Mean Range	 47.8 35.6, 63.8	 35.8 31.5, 39.2	 34.4 29.4, 42.8
Time-to-event (in days) Mean Median Min, max	 116.5 170 1, 699	 103.4 90 58, 517	 181.4 146.5 54, 401

During the second randomization, the following suicidality events occurred:

Table 17: Suicidality Events Occurring During Second Randomization

STUDY#/ PATIENT ID #	RANDOMIZATION	AE DOSE	TTE	C-CASA
EFC4743 004743840031008	PLB/PLB	PLB	575 days	4
EFC4743 004743840031047	PLB/PLB	PLB	742 days	4
EFC4743 004743840035073	5 mg/PLB	PLB	526 days	4
EFC4743 004743124021039	5 mg/5 mg	5 mg	406 days	4
EFC4743 004743840063084	5 mg/5 mg	5 mg	477 days	4
EFC4796 004796840031074	5 mg/5 mg	5 mg	364 days	4
EFC4796 004796840031191	20 mg/5 mg	5 mg	270 days	2
EFC4743 004743840023054	20 mg/PLB	PLB	464 days	9
EFC4796 004796840019065	20 mg/20 mg	20 mg	161 days	3
EFC4796 004796840021011	20 mg/20 mg	20 mg	272 days	4

Roughly 50% of the subjects in the rimonabant and placebo groups withdrew early from the trials, with more rimonabant subjects doing so due to depression, anxiety, mood alteration with depressive symptoms, and the need for antidepressant medication. Given the lack of systematic follow-up of these subjects and rimonabant's long half-life (~16 days on average), the results of the above analyses should be viewed as incomplete at best and at worse as an underestimate of rimonabant's risk for suicidality.

According to Sanofi-Aventis, in ongoing trials as of the December 18, 2006 cut-off date, data were available on 17 unblinded cases of suicidality - 11 on rimonabant 20 mg and 6 on placebo. The rimonabant 20 mg cases included 1 completed suicide, 1 self-injurious ideation, 8 suicidal ideations, and 1 depression suicidal; the placebo cases included 2 suicide attempts and 5 suicidal ideations**.** It should be noted that the Division had also received 2 additional reports during this time period - one of "homicidal ideation" in a subject receiving rimonabant 20 mg in study PMC_0172 and one of suicide attempt in a

subject receiving rimonabant 20 mg in study EFC5823. Subsequent to the sponsor's submission of the safety update in March 2007, the following reports of suicidality have been received: 2 reports of suicide attempt - one in a 60-year-old female randomized to 20 mg rimonabant in the CRESCENDO trial and one in a 56-year-old male randomized to rimonabant 20 mg in the CRESCENDO trial; a report of a suicide gesture in a 37-year-old female randomized to 20 mg rimonabant in the RAPSODI trial; and a report of suicidal ideation in a 64-year-old female randomized to 20 mg rimonabant in the CRESCENDO trial.

It should be noted that in the entire rimonabant clinical trial database, there have been 2 completed suicides – one in RIO North America in a subject taking rimonabant 5 mg and one in the ongoing study STRADIVARIUS in a subject taking rimonabant 20 mg.

Provided in the Appendix is a summary of those subjects from the RIO and SERENADE trials who were reported as possible or definite cases of suicidality (during first randomization only), along with their associated psychiatric symptoms as derived from the datasets, case report forms, and patient narratives.

B. Concurrent Use of Anti-Obesity and Anti-Depressant Medication

As noted earlier in this document, all patients who were placed on anti-depressant therapy were to be discontinued from the RIO studies. This was done to avoid confounding the weight-loss data. Given the increased incidence of depression-related adverse events in subjects treated with rimonabant 20 mg vs. placebo and the lack of data on the efficacy and safety of concomitant use of rimonabant with anti-depressants, the Division obtained concurrency prescription-use data for anti-obesity and anti-depressant medication. During the time period covering 2004 through 2006, roughly 580,000 raw patients per year received a prescription for one of the following weight-loss drugs: phentermine, orlistat, sibutramine, or diethylpropion. Approximately 30% of these raw patients received a concurrent prescription for an anti-depressant medication.[6]

C. Neurological Adverse Events

CB_1 receptor density is particularly high in the cerebellum, cortex, hippocampus, hypothalamus, and basal ganglia – areas of the brain that affect memory, motor function, and reward behaviors. They are also present on the peripheral nerves where they play a neuroprotective role. Neurological symptoms, including sensory changes, motor impairments, and cognitive difficulties appeared commonly in the clinical trials, but were not well characterized or evaluated in detail. Sanofi-Aventis was asked to provide additional data from ongoing and/or future trials in which appropriate attention was given to capturing and following-up on treatment-emergent neurological symptoms.

Neurological symptoms, while vague, occurred with greater frequency in rimonabant 20

6 Verispan Vector One®: Concurrency, data extracted 3-12-07

mg treated patients than in placebo patients: 27.4% and 24.4% respectively. Among subjects treated with rimonabant 20 mg, the most commonly reported neurological symptoms were: headache (10%), dizziness (8.6%), and paresthesia/hypoaesthesia/dysaesthesia (3.3%); while among subjects treated with placebo, the most commonly reported neurological symptoms were: headache (12.7%), dizziness (5.6%), paresthesia/hypoaesthesia/dysaesthesia (2.1%) (Table 18 and Figure 6).

Dizziness and vertigo occurred with greater frequency in the rimonabant 20 mg group than in the placebo group – 9.6% and 6.1%, respectively. Motor impairment occurred with greater frequency in the rimonabant 20 mg group than in the placebo group – 1.7% and 0.12%, respectively – and was driven predominantly by "tremor" and "balance disorder". Cognitive disorders occurred with greater frequency in the rimonabant 20 mg group than in the placebo group – 3.5% and 2.0%, respectively – and were driven predominantly by "mental impairment", "somnolence", and "disturbance in thinking/perception". These neurological adverse events may well have contributed to the disproportionate number of subjects who sustained injuries (contusions, concussions, falls, road traffic accidents, whiplash, and injuries) during the RIO trials in the rimonabant 20 mg group (6.9%) vs. the placebo group (3.8%).

Paresthesia, dysaesthesia, and hypoaesthesia occurred with slightly greater frequency in the rimonabant 20 mg group than in the placebo group – 3.3% and 2.1%, respectively. However, when the studies in diabetic patients were analyzed separately, the occurrence of these symptoms was much greater in the rimonabant 20 mg group vs. placebo. In RIO-Diabetes and in SERENADE (conducted in treatment-naïve Type 2 diabetics) – approximately 5% of rimonabant 20 mg treated subjects vs. 1.2% of placebo treated patients experienced paresthesia, dysaesthesia, or hypoaesthesia.

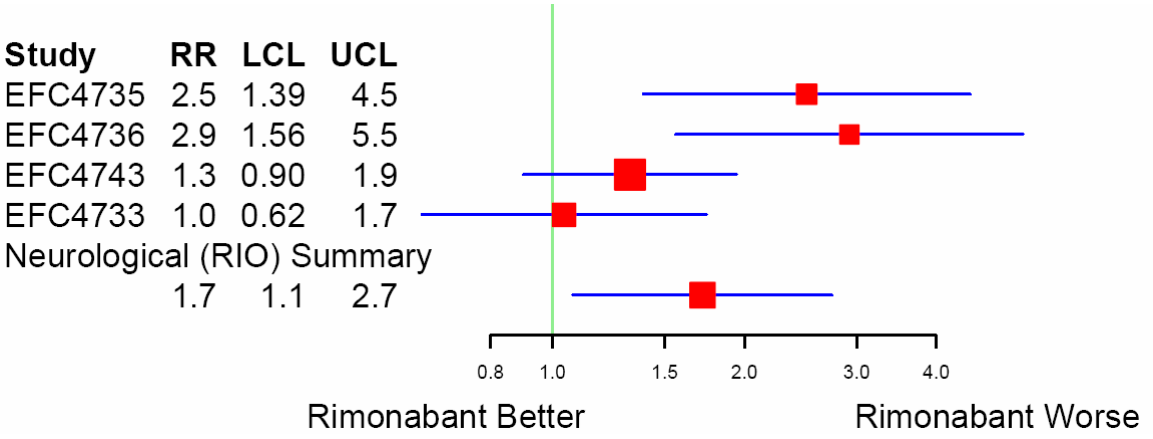
Table 18: Neurological Adverse Events - Pooled RIO studies

AEHLGTN PREFERRED TERM	**PLACEBO N=1602 (%)**	**5 MG N=2220 (%)**	**20 MG N=2176 (%)**
Total # of subjects reporting a symptom	**391 (24.4)**	**535 (24.1)**	**596 (27.4)**
Neurological Disorders NEC	**151 (9.4)**	**227 (10.2)**	**311 (14.3)**
Dizziness	89 (5.56)	138 (6.22)	186 (8.55)
Paresthesia	17 (1.06)	23 (1.04)	37 (1.70)
Hypoaesthesia	14 (0.87)	32 (1.44)	31 (1.42)
Headaches	**247 (15.4)**	**287 (12.9)**	**266 (12.2)**
Headache	203 (12.67)	225 (10.14)	220 (10.11)
Migraine	31 (1.94)	43 (1.94)	36 (1.65)
Mental Impairment Disorders	**21 (1.3)**	**26 (1.2)**	**45 (2.1)**
Memory impairment	7 (0.44)	14 (0.63)	16 (0.74)
Disturbance in attention	10 (0.62)	2 (0.09)	15 (0.69)
Amnesia	8 (0.50)	8 (0.36)	14 (0.64)
Spinal Cord and Nerve Root Disorders	**15 (0.94)**	**29 (1.3)**	**31 (1.4)**
Sciatica	10 (0.62)	23 (1.04)	27 (1.24)
Movement Disorders (incl Parkinsonism)	**1 (0.06)**	**8 (0.36)**	**24 (1.1)**

AEHLGTN PREFERRED TERM	PLACEBO N=1602 (%)	5 MG N=2220 (%)	20 MG N=2176 (%)
Tremor	0	6 (0.27)	21 (0.97)
Peripheral Neuropathies	**19 (1.19)**	**29 (1.31)**	**21 (0.97)**

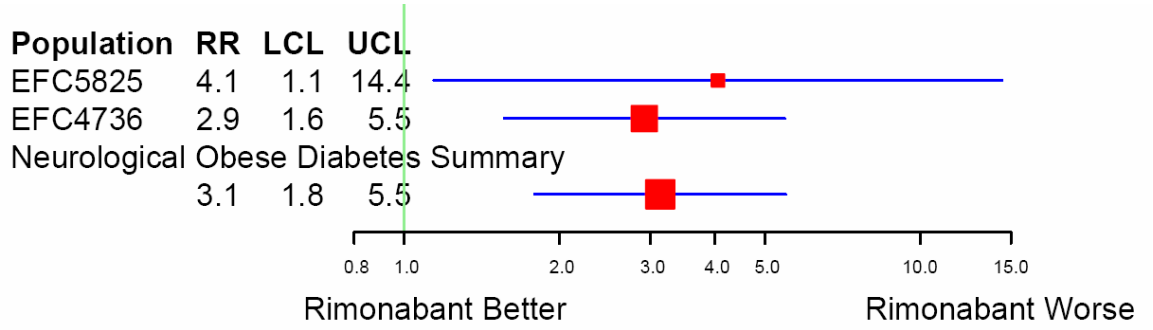
Subjects receiving the same treatment during the whole study

Figure 6: Relative Risk for Neurological Adverse Events – Rimonabant 20 mg vs. Placebo – RIO Studies



In RIO Diabetes and SERENADE, the overall relative risk (CI) for the incidence of a neurological adverse event for rimonabant 20 mg vs. placebo was 3.1 (1.8, 5.5).

Figure 7: Relative Risk for Neurological Adverse Events - Rimonabant 20 mg vs. Placebo - Diabetes Studies



When multiple sclerosis is induced by viral inoculation in CB_1 knockout mice or in mice treated with a CB_1 receptor antagonist the neurodegenerative process is more severe. This suggests that CB_1 antagonism may exacerbate inflammatory demyelinating diseases in humans.[7]

7 Pacher P et al. The Endocannabinoid System as an Emerging Target of Pharmacotherapy. *Pharmacological Reviews.* 2006;58:389-462.

Five cases of confirmed multiple sclerosis (3) or suspicion of demyelinating disease (2) have been reported from rimonabant trials as of 18 December 2006. Of these, 1 (0.05%) was in a patient on placebo; 2 were in patients on rimonabant 5 mg (0.09%); and 2 were in patients on rimonabant 20 mg (0.05%). The 2 subjects on rimonabant 20 mg who were suspected of having MS were both from smoking cessation trials (1 of them had a medical history of MS, but experienced exacerbation of her symptoms on rimonabant); the other 3 subjects were from obesity trials. One of the cases of multiple sclerosis from the obesity trials was published as a case report.[8] This case was notable because recovery to near normal was noted within weeks after discontinuation of rimonabant treatment.

D. Seizures

Cannabinoids possess anticonvulsant properties and the endocannabinoid system has been implicated in regulating seizure duration and frequency. It is speculated that epileptiform seizure activity elicits an increase in the "on-demand" synthesis of endocannabinoids resulting in increased activation of presynaptic CB_1 receptors with subsequent regulation of neuronal hyperexcitability and seizure termination. In animals, rimonabant accumulates in the brain with multiple dosing, therefore AUC/C_{max} ratios probably over-estimate safety margins in humans.

In preclinical evaluations, approximately 6% of rats and mice and 20% (2/10) of monkeys developed seizures while receiving long-term treatment with doses of rimonabant 0.5-2 times the 20 mg dose proposed for marketing. Approximately 1.5% of control mice developed seizures, while none of the control rats or monkeys did so.

Nineteen cases of seizure were reported in the completed rimonabant clinical trials. Of these, three were excluded from the analyses – 2 cases that occurred during placebo run-in and one case that occurred > 3 months after dosing. Of the remaining sixteen, eleven were adjudicated as "likely" or "possible" by 2 independent neurologists: 6 cases in rimonabant 20 mg groups (5 in obesity trials; and 1 in a smoking cessation trial), 2 cases in the rimonabant 5 mg groups (both in obesity trials), and 3 cases in the placebo groups (1 in an obesity trial; 1 in a smoking cessation trial; and 1 in the schizophrenia trial) (Table 19).

Table 19: Incident Rates of Seizure in Phase 2 and 3 Rimonabant Studies

STUDY	POPULATION	RIMONABANT 20 MG	RIMONABANT 5 MG	PLACEBO
ACT4855	alcohol dependence	0/26.2	-	1/23.5 (4.26)
METATRIAL	Schizophrenia	0/4	-	2/5.7 (35.09)

8 Oosten BW, et al. Multiple sclerosis following treatment with a cannabinoid receptor-1 antagonist. *Multiple Sclerosis*. 2004;10:330-331.

STUDY	POPULATION	RIMONABANT 20 MG	RIMONABANT 5 MG	PLACEBO
Other total		0/30.2		3/29.2 (10.27)
PDY3796	Obesity	-	-	0/1.6
DRI3388	Obesity	0/18.6	0/17.1	0/16.5
EFC4733	Obesity	1/761.8 (0.13)	1/794.5 (0.13)	0/377.8
EFC4743	Obesity	3/1154.3 (0.26)	1/1081.2 (0.09)	1/1172.5 (0.09)
EFC4735	Obesity	0/266.8	0/262.3	0/268.2
EFC4736	Obesity	2/269.4 (0.74)	0/283.6	0/277.7
ACT3801	Obesity	0/57.9	-	0/59.9
EFC5031	Obesity	0/16.5	-	0/18.1
EFC5745	Obesity	0/3.1	-	0/3.1
EFC5825 (SERENADE)	Obesity	1/59.6 (1.68)	-	0/63.9
Obesity Total		7/2608 (0.27)	2/2438.7 (0.08)	1/2259.3 (0.04)
ACT4389	Smokers	-	-	0/28.6
EFC4964 STRATUS-US	Smokers	0/43	0/42.3	0/42.9
EFC4474 STRATUS-EU	Smokers	0/41.5	0/39.6	0/41.1
EFC5794 STRATUS-META	Smokers	0/42	-	0/43.8
EFC4796 STRATUS-WW	Smokers	1/653.5 (0.15)	0/684.2	1/366.3 (0.27)
EFC4798 CIRRUS	Smokers	1/109.1 (0.92)	-	-
Smokers Total		2/889.1 (0.22)	0/766.1	1/522.7 (0.19)
Grand Total		9/3527.3 (0.26)	2/3204.8 (0.06)	5/2811.2 (0.18)

Analysis of the 11 cases of "likely"/"possible" seizure revealed the following characteristics:

- The average age of a subject experiencing a seizure was 38.3 years for placebo-treated subjects; 46 years for subjects treated with rimonabant 5 mg; and 42.5 years for subjects treated with rimonabant 20 mg. For obesity studies only, the average age was 45 years, 46 years, and 43.4 years, respectively.

- The mean time-to-event (TTE) (range) was 84.7 days (10-191) for placebo treated subjects; 123 days (63-183) for rimonabant 5 mg treated subjects; and 135.2 days (27-416) for rimonabant 20 mg treated subjects. For obesity studies only, the mean TTE (range) was 53 (53), 123 (63-183) and 156.8 (28-416), respectively.
- All of the cases of seizure in the obesity studies occurred in females – 5 on rimonabant 20 mg, 2 on rimonabant 5 mg, and 1 on placebo; the three other cases of seizure were in males – 1 on rimonabant 20 mg and 1 on placebo in smoking cessation studies, and 1 on placebo in the schizophrenia study.

There have been 8 cases of seizure reviewed by independent experts in the ongoing studies – 6 on rimonabant 20 mg and 2 on placebo.

Statistical analyses of the seizure data will be provided during the oral presentation at the Advisory Committee meeting.

Cases of seizure are summarized in the Appendix.

10. Post-Approval Safety Data

Sanofi-Aventis submitted a periodic safety update report (PSUR) for the time period June 19, 2006 to December 18, 2006. Rimonabant 20 mg once-daily is currently approved in more than 30 countries in Europe, America, and Asia. It has been launched in 9 European countries, as well as in Argentina. From launch to 30 November 2006, the estimated worldwide post-marketing exposure was 78,610 treated patients, mainly in Germany and in the United Kingdom. The following table summarizes the sales data and patient exposure provided by the sponsor.

Table 20: Rimonabant Sales Data and Patient Exposure

19-Jun-2006 to 30-Nov-2006		
Countries	**Number of tablets sold**	**Number of exposed patients**
Argentina	98,000	840
Austria	48,000	1,400
Denmark	140,000	4,420
Finland	110,000	2,010
Germany	1,987,000	48,330
Ireland	38,472	1,100
Norway	100,000	1,160
Sweden	170,000	3,370
United Kingdom	1,275,000	15,980
Total	**3,966,472**	**78,610**

During the reference period of the first PSUR (19 June 2006 to 18 December 2006), 918 spontaneous cases were reported to the Marketing Authorization Holder (MAH):

- 386 cases were received from healthcare professionals, either directly (n=383) or through Regulatory Authorities, of which 67 were serious. Fifty-three of these cases referred to serious and unlisted first main reactions.
- 532 cases were received from consumers, of which 15 were serious.

It is noteworthy that 387 out of these 918 spontaneous cases were stimulated reports, initially received through phone calls issued by call centers dedicated to patients' support programs in the U.K. and Ireland. The vast majority of the 918 spontaneous reports came from the U.K. (n=627) and Germany (n=206).

There were a total of 2362 adverse reactions associated with these 918 cases. The most frequently reported adverse reactions were of gastrointestinal (209 medically confirmed; 320 consumer reports), nervous system (143 medically confirmed; 154 consumer reports) or psychiatric (308 medically confirmed; 169 consumer reports) origins. The most frequent adverse reactions within these categories are summarized below:

- Gastrointestinal adverse reactions: nausea (47.4%), diarrhea (16.8%), and vomiting (10.2%)
- Psychiatric adverse reactions: anxiety (10.7%), depressed mood (10.7%), depression (10.3%), and insomnia (7.3%)

- Nervous system adverse reactions: dizziness (27.6%), headache (17.8%), paresthesia (5.7%), tremor (5.1%), somnolence (4.4%), amnesia (4.0%), and disturbance in attention (3.7%)

Post-marketing data reveal that reports of nervous system disorders are frequent (15% of adverse events reported) and are driven predominantly by "dizziness". Sanofi-Aventis has detected signals for the previously unlisted preferred terms "disturbance in attention" and "tremor".

The Division has received one report of a post-marketing case of optic neuritis in a subject who had been taking rimonabant 20 mg for approximately one month; MRI report indicated "could be MS". The age of the subject is unknown. Another case of a 42-year-old female with a history of MS who experienced an exacerbation of her symptoms while on rimonabant 20 mg has also been received.

Post-marketing data has revealed two additional case of seizure associated with the use of rimonabant 20 mg. Another case of "moderate, uncontrollable tonic/clonic extra-pyramidal movement of the head" associated with rimonabant 20 mg use remains suspect.

Post-marketing data reveal 6 medically confirmed spontaneous reports of suicidal ideation and 3 consumer reports.

The Division of Metabolism and Endocrine Products has been maintaining a log of all adverse event reports submitted to the Agency by Sanofi-Aventis. As of May 11, 2007, the Division had received 15 reports of suicidal ideation associated with rimonabant use in the post-marketing setting. Other reports of note are 4 reports of delusional symptoms, 6 reports of psychotic behavior (including a man who attempted to strangle his daughter), and 5 reports of aggression (including a man who beat his wife.)

APPENDIX A:

Summary of all deaths occurring in completed studies and ongoing studies

STUDY #	USUBJID	AGE/SEX	CAUSE	TREATMENT	STUDY DAY
Obesity studies					
EFC4733	004733250201018	55/F	Uterine adenocarcinoma	20 mg	40
EFC4736	004736246603015	59/F	Automobile accident (passenger)	20mg	196
EFC4736	004736616604027	52/M	Acute cardiac insufficiency	20 mg	56
EFC4736	004736826603021	58/M	Coronary artery disease	20 mg (within 30 days of treatment end)	155
EFC4736	004736840685028	55/M	Septic shock	5 mg	181
EFC4743	004743840073075	19/F	Cardiac arrest	5 mg	172
EFC4743	004743840013019	63/M	Suicide	5 mg (within 30 days of treatment end)	157
EFC4743	004743840039039	75/F	Acute Pulmonary embolus	20 mg→ Placebo (within 30 days of treatment end)	709
EFC4733	004733528202009	63/F	Cerebral hemorrhage	Placebo	76
EFC5825	005825840022004	60/F	Subdural hemorrhage	Placebo	~77
Smoking cessation studies					
EFC4796	004796124004012	37/M	Automobile accident ("alcoholemia")	20 mg	60
EFC4796	004796840018026	56/M	Atherosclerotic cardiovascular disease	20 mg	29
EFC4796	004796840032084	61/F	Cardiopulmonary arrest	5 mg→ Placebo (>75 days post-treatment change; <30 days post treatment end)	381
Deaths occurring outside of treatment window					
EFC4736	004736203602002	58/M	Myocardial infarction	20 mg (>75 days post treatment)	965
EFC4798	004798840011030	64/M	Acute respiratory distress syndrome	20 mg (>75 days post-treatment)	139
EFC4733	004733528203030	55/M	Cerebrovascular	Placebo	793

STUDY #	USUBJID	AGE/SEX	CAUSE	TREATMENT	STUDY DAY
			accident	(>75 days post-treatment)	
EFC4736	004736840611010	56/M	Cardiac arrest	Placebo run-in (pre-treatment)	0
Deaths occurring in ongoing studies					
EFC5827	005827124001102	36/M	Completed suicide	20 mg	~300
EFC5826	005826840150005	62/M	Acute renal failure/sepsis/CHF	Placebo	~30
EFC5827	005827840057002	49/M	Motor vehicle accident/ASHD	Screening	0
EFC5593	005593840006001	75/M	Embolic stroke	Blind	~42
EFC5826	005826840087001	68/F	Brain tumor	Blind	~14
EFC5827	005827840013006	56/F	Acute myeloid leukemia	Blind	~330
EFC5827	005827616003008	61/M	Gastrointestinal hemorrhage	Blind	~210
EFC5107	005107840026082	75/F	Myocardial infarction	Blind	Unk
EFC5828	005828528003077	62/M	Esophageal adenocarcinoma	Blind	90
EFC5826	005826840043011	71/M	Malignant hypertension/acute renal failure/CVA	Blind	1
EFC5826	005826826003001	84/F	Gastric bleeding	Blind	90
EFC5826	005826410104006	70/F	Spinal compression fracture secondary to fall; stroke	Blind	56

APPENDIX B:

Cases of seizure – completed studies

STUDY ID	DOSE	AGE/GENDER	TIME TO ONSET (IN DAYS)	RELEVANT HISTORY	EEG RESULT	PATIENT POPULATION IN STUDY
Cases adjudicated as "possible" or "likely"						
EFC4733**	20 mg	29/Female	416	LOC after drinking; ?h/o tetany	Normal	Obese
EFC4736**	20 mg	48/Female	138	History of petit mal seizure	Abnormal	Diabetics
EFC4743***	20 mg	25/Female	121	h/o MVA with head injury 2 years prior; rx'd with alprazolam for 25 days, then none for 11 days	Normal	Obese
EFC4743**	20 mg	56/Female	28	h/o seizure disorder	Not done	Obese
EFC5825***	20 mg	59/Female	81	Frontal meningioma	Not done	Diabetics
EFC4743***	5 mg	48/Female	63	None	Abnormal	Obese
EFC4733***	5 mg	44/Female	183	h/o epilepsy 10 years before	Abnormal	Obese
EFC4743***	Placebo	45/Female	53	h/o epilepsy	Not done	Obese
EFC4798***	20 mg	38/Male	27	Suicide attempt with bupropion	Not done	Smokers
EFC4796***	Placebo	39/Male	191 (120 post re-randomization from 5 mg)	h/o seizure; astrocytoma	Not done	Smokers
METATRIAL***	Placebo	31/Male	10	Polysubstance abuse	Normal	Schizophrenics
Cases adjudicated as "possible" or "likely" – occurring outside treatment window						
EFC4736***	Placebo run-in	56/Male	0	Cardiac arrest with hypoxic seizure	Not done	Diabetics
EFC4743***	Placebo run-in	43/Female	16	Polysomnogram – sleep apnea induced	Normal	Obese
EFC4796**	Placebo	67/Female	456 (3 months post dosing)	Syncope at hair dresser's; sweaty before	Negative	Smokers
Cases adjudicated as "unlikely"						
EFC4736	20 mg	44/Female	420	None	Abnormal	Diabetics
EFC4743	20 mg	53/Female	203/328	Described as lips numb/clonus	Not done	Obese
EFC4796	20 mg	46/Female	22	?Hand tremor	Not done	Smokers
ACT4855	Placebo	47/Female	60	Alcohol relapse – "twitching"	Not done	Alcoholics

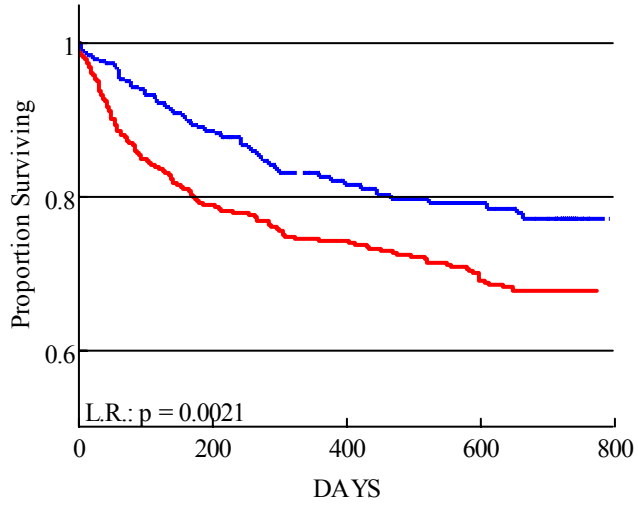
STUDY ID	DOSE	AGE/GENDER	TIME TO ONSET (IN DAYS)	RELEVANT HISTORY	EEG RESULT	PATIENT POPULATION IN STUDY
METATRIAL	Placebo	53/Female	40	Hospitalized for psychosis; felt dizzy; LOC for 1 minute	Negative	Schizophrenics
Cases from ongoing studies:						
EFC5826	20 mg	58/Male	98	h/o recent stroke	Low potential voltage alpha without focus and without epileptic potentials	Abdominally obese with clustering risk factors
EFC5826	20 mg	?/?	165, 195	h/o pituitary tumor and treatment for myoclonic seizure	Not done	Abdominally obese with clustering risk factors
EFC5827	20 mg	46/Male	42, 44, 48	h/o seizures	Not done	Overweight with clustering

**** Seizure adjudicated as possible** ***** Seizure adjudicated as likely**

APPENDIX C: Kaplan-Meier curves – Time to first psychiatric adverse event

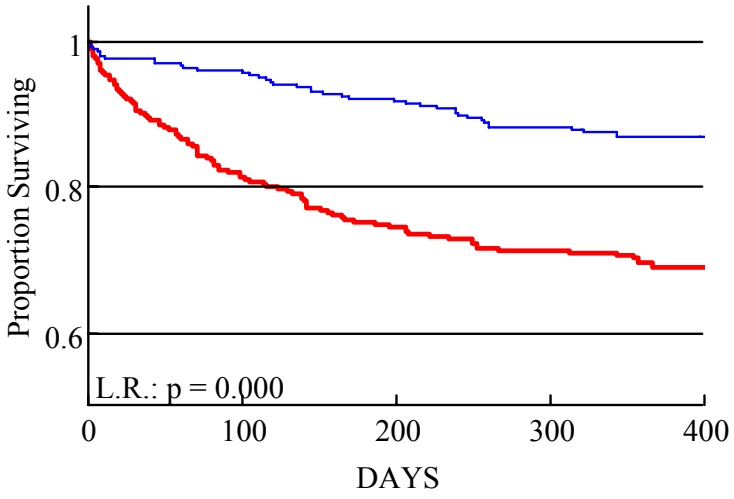
RIO-Europe

STUDYID
EFC4733



RIO-Lipids

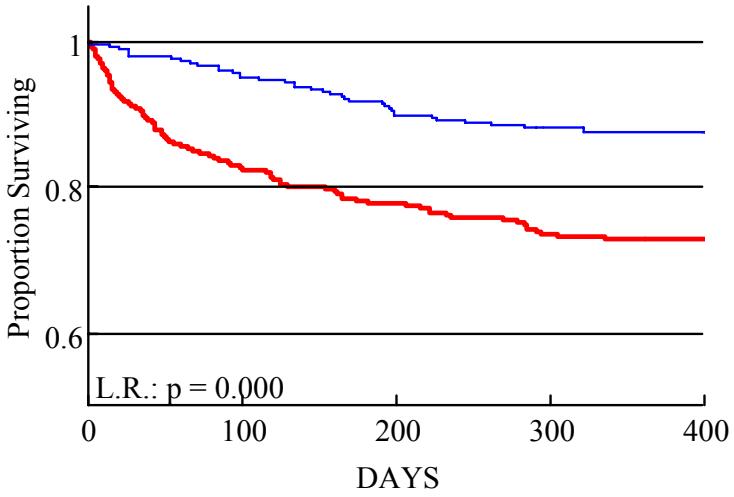
STUDYID
EFC4735



ACTRTGRP:
20 mg
PLB

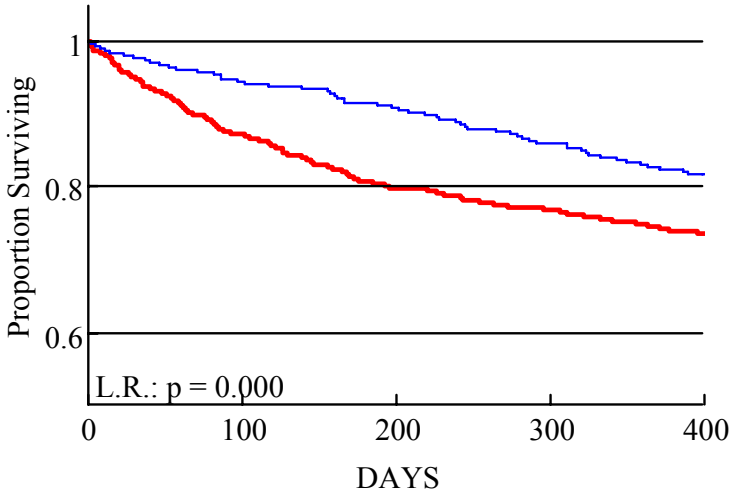
RIO-Diabetes

STUDYID
EFC4736



RIO-North America

STUDYID
EFC4743



ACTRTGRP:
20 mg
PLB

APPENDIX D:

Cases of suicidality and associated symptoms – Obesity studies

EFC4733 – RIO-Europe

USUBJID	DOSE	COLUMBIA CODE	ASSOCIATED SYMPTOMS
004733056201038	20 mg	4	Psychomotor retardation; irritability; fear; worry a lot. Depression; nightmare; sleep disorder.
004733246201033	20 mg	4	Psychomotor retardation; psychomotor agitation or excessive motor activity Insomnia
004733246204005	20 mg	4	Anxiety disorders Nightmare; depression
004733528202015	20 mg	4	Psychomotor retardation; aggressivity; feeling of worthlessness; excessive guilt; self-inflicted or accidental injuries Irritability
004733840214017	20 mg	4	Psychomotor retardation; psychomotor agitation or excessive motor activity; anxiety disorders; feeling of worthlessness; excessive guilt; palpitations Mood swings; adjustment disorder with mixed anxiety and depressed mood; hallucinations.
004733250207005	20 mg	9	Psychomotor retardation; anxiety disorders; self-inflicted or accidental injuries Severe depression
004733840215014	Placebo	4	None

EFC4735 – RIO-Lipids

USUBJID	DOSE	COLUMBIA CODE	ASSOCIATED SYMPTOMS
004735124404079	20 mg	4	Psychomotor agitation or excessive motor activity; anxiety

USUBJID	DOSE	COLUMBIA CODE	ASSOCIATED SYMPTOMS
			disorders; excessive guilt Adjustment disorder with mixed anxiety and depressed mood; over-excited and anxious
004735840423025	20 mg	4	Psychomotor agitation or excessive motor activity Depressed mood; insomnia
004735124441049	20 mg	4	Psychomotor retardation; anxiety disorders; anhedonia Depression; loss of sleep
004735124409017	5 mg	4	Feeling of worthlessness; excessive guilt; irritability; fatigue. Depression
004735840423028	5 mg	4	Psychomotor agitation or excessive motor activity; aggressivity; feeling of worthlessness; irritability; problems with concentration Major depression
004735840434027	Placebo	4	Anxiety disorders; mania; irritability; decreased concentration and memory; decreased energy and motivation Bipolar disorder – mania followed by depression
004735124404086	Placebo	4	Anxiety disorders; irritability Personality disorder; adjustment disorder with mixed anxiety/depression

EFC4736 – RIO-Diabetes

USUBJID	DOSE	COLUMBIA CODE	ASSOCIATED SYMPTOMS
004736124615002	20 mg	4	Tearful Depressive symptom
004736826611013	20 mg	4	Excessive guilt Major depression

EFC4743 – RIO-North America

USUBJID	DOSE	COLUMBIA CODE	ASSOCIATED SYMPTOMS
004743124021003	20 mg	4	Psychomotor retardation; feeling of worthlessness; amotivation. Major depression
004743124070036	20 mg	4	Anxiety disorders; aggressivity; paranoid reaction; sad/crying/loss of libido; irritability Anxiety; depression; poor sleep; anger; nervousness
004743840012069	20 mg	4	Psychomotor agitation or excessive motor activity; anxiety disorders; insomnia Depression; panic attack
004743840018024	20 mg	4	Anxiety disorders; anhedonia Depression; sleeplessness; "negligible homicidal potential"
004743840027001	20 mg	4	Psychomotor retardation; anxiety disorders; feeling of worthlessness; tremor; decreased libido; tearful; sad Depression
004743840029058	20 mg	4	Depressed mood
004743840032051	20 mg	4	Anxiety disorders; feeling of worthlessness Adjustment disorder with mixed anxiety and depressed mood; decreased sleep
004743840012031	5 mg	4	Obsessional Depressed mood
004743840055014	5 mg	4	Depression
004743840013019	5 mg	6	Insomnia Depression
004743840029066	5 mg	4	Depressed mood; irritability; restlessness
004743840068037	Placebo	9	None
004743840006002	Placebo	4	Feeling of worthlessness; hopeless feeling/not interested/irritability Bipolar II disorder
004743840026033	Placebo	4	Psychomotor retardation; tearful
004743840034010	Placebo	4	Irritability/premenstrual dysphoric component Depression

EFC5825-SERENADE

USUBJID	Dose	Columbia code	Associated symptoms
005825276002016	20 mg	4	Anxiety disorders; melancholic symptoms

Statistical Review of Safety: Division of Biometrics II

Rimonabant Briefing Document

Endocrine and Metabolic Drugs Advisory Committee Meeting

June 13, 2007

NDA 21-888

Sponsor: Sanofi-Aventis U.S. Inc.

Statistical Reviewer: Lee-Ping Pian, Ph.D.

Statistical Team Leader: Todd Sahlroot, Ph.D.

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

On October 26, 2006 Sanofi-Aventis U.S. Inc submitted a complete response to the NDA #21-888 approvable action letter to address safety concerns.

During the development of rimonabant, the sponsor conducted 2 separate phase 3 programs: the RIO program (Rimonabant in Obesity) for metabolic and obesity indications, and the STRATUS program (Studies with Rimonabant and Tobacco Use) for the smoking cessation and maintenance of abstinence indications. The 5 mg and 20 mg doses of rimonabant were the 2 main doses studied in the phase 3 programs. The proposed dose for marketing was 20 mg rimonabant. Rimonabant was not efficacious for the smoking cessation; hence it was not approved for that indication. For the obesity indication, 20 mg rimonabant was deemed efficacious but there were central nervous system (CNS) safety concerns; hence the Agency issued an approvable letter pending additional information.

The specific safety adverse events of interest are suicidality-related events, psychiatric events, neurological events and seizures. The suicidality-related events were reevaluated and updated for the NDA resubmission.

The purpose of this review was to estimate the effect size of rimonabant versus placebo on the above mentioned safety outcomes across multiple studies in the overall population, and especially in the referral population consisting of the obese and obese diabetic populations in phase 2 and phase 3 clinical trials. The primary analysis approaches combined data across studies using methods that preserved 'study' as a unit of analysis. The primary objective was the analysis of suicidality adverse events and the secondary objectives were the analyses of psychiatric events, neurological events, and seizures.

1.1 CONCLUSIONS AND RECOMMENDATIONS

The incidence of suicidality – specifically suicidal ideation – was higher for 20 mg rimonabant compared to placebo. Similarly, the incidence of psychiatric adverse events, neurological adverse events and seizures were consistently higher for 20 mg rimonabant compared to placebo. Tables 1 to 3 below display risk estimates and the 95% confidence intervals for the overall population, the obesity population and the obese diabetic population for the incidence of suicidality, psychiatric and neurological events, and seizures, respectively.

Table 1 Odds ratios and risk difference for incidence of Suicidality for 20 mg rimonabant versus placebo

Population	Suicidality OR	Suicidality RD (%)
Overall	2.0 [1.2, 3.4]	0.34 [0.14, 0.54]
Obesity	**2.0 [0.9, 5.1]**	**0.32[-0.12, 0.76]**
Diabetes	*	0.62 [-0.27, 1.5]

*no events in the placebo group, therefore, OR estimate is ∞
OR=odds ratio
RD=risk difference

Table 2 Risk ratio for incidence of psychiatric AEs and neurological AEs for 20 mg rimonabant versus placebo

Population	Psychiatric RR	Neurological RR
Overall	1.6 [1.4, 1.9]	1.5 [1.3, 1.7]
Obesity	**1.9 [1.5, 2.3]**	**1.9 [1.2, 2.9]**
Diabetes	2.0 [1.5, 2.7]	3.1 [1.8, 5.4]

RR=risk ratio

Table 3 Odds ratio & Risk difference for incidence of seizure for 20 mg rimonabant versus placebo

Population	Seizure OR	Seizure RD
Overall	1.2 [0.4, 4.2]	0.0017 [-0.1, 0.1]
Obesity	**4.8 [0.7, 110]**	**0.13 [-0.15, 0.4]**
Diabetes	*	0.62 [-0.27, 1.5]

*no events in the placebo group, therefore, estimate is ∞

2. INTRODUCTION

2.1 OVERVIEW

Table 4 displays the 18 studies completed and submitted up to March 2007. Of the 18 completed studies, 14 contributed to the suicidality meta-analysis. For the suicidality meta-analysis the duration of study was not used to exclude studies from the analysis but a small sample size or lack of a control group were. Duration was not a limiting factor for inclusion in the analysis because the smallest duration of the phase 2 and phase 3 trials was 4 weeks and there was no evidence of a delayed onset for the adverse events of interest. The estimates from very small studies were very unstable especially for relatively rare events. The studies excluded were a small clamp study EFC5745 (n=20 per group) and 3 studies without a valid second treatment group (PDY3796, ACT4389 and EFC4798).

For studies with more than one randomization (EFC4743, EFC4796), only the first randomization period was included in the analysis. This reviewer conducted sensitivity analyses that included the additional events that occurred during any second randomizations (Section 2.3).

Table 4 Phase 2 and Phase 3 Clinical Trials of Rimonabant

Protocol # (Phase)	Suicidality	Type of Patient Study	**20 mg n**	**5 mg n**	**Plb n**	Treatment Duration (Weeks)
ACT4855 (ACTOL) (PHASE 2)	Y	Alcoholic Patients	131	.	127	12
METATRIAL (DFI3024,3067,3077,3138) (Phase 2)	Y	Schizophrenic patients	72	.	98	6
Other Total			203		225	

Protocol # (Phase)	Suicidality	Type of Patient Study	**20 mg n**	**5 mg n**	**Plb n**	Treatment Duration (Weeks)
PDY3796*** (Phase 2)	N	Obese patients	.	.	22	4
ACT3801* (CRAVING) (Phase 3)	Y	Obese patients with eating disorder	143	.	146	26
DRI 3388 (Phase 2)	Y	Obese patients	69	67	73	16
EFC5745* (CLAMP) (Phase 3)	N	Overweight and obese patients with insulin resistance	20	.	20	8
EFC5031* (REBA) (Phase 3)	Y	Obese patients energy intake	76	.	80	12
EFC4735 (RIO LIPIDS) (Phase 3)	Y	Overweight & obese dyslipidemics	346	345	342	52
EFC4736 (RIO DIABETES) (Phase 3)	Y	overweight & obese diabetics	339	358	348	52
EFC4733 (RIO EUROPE) (Phase 3)	Y	Obese patients	599	603	305	104
EFC4743 (RIO NA) (Phase 3)	Y	Obese patients	1219(Y1) 333(Y2)	1214(Y1) 300(Y2)	607(Y1) 924(Y2)	52 Re-randomized for 2nd year
EFC5825** (SERENADE)	Y	Obese patients	138		140	26
Total Obesity			**2949**	**2587**	**2083**	
ACT4389*** (Phase 2)	N	Smokers	.	.	183	10
EFC4796 (STRATUS WW) (Phase 3)	Y	Smokers	3023 (W1-10) 340 (W11-2)	2016 (W1-10) 657 (W11-52)	664 (W11-52)	52
EFC5794 (STRATUS META) (Phase 3)	Y	Smokers	262	.	268	10
EFC4474 (STRATUS EU) (Phase 3)	Y	Smokers	267	256	260	10
EFC4964 (STRATUS US) (Phase 3)	Y	Smokers	261	262	261	10

Protocol # (Phase)	Suicidality	Type of Patient Study	**20 mg n**	**5 mg n**	**Plb n**	Treatment Duration (Weeks)
EFC4798*** (CIRRUS) (Phase 3)	N	Smokers	754	.	.	9
Smokers Total			**4567**	**2534**	**972**	
Grand Total			**7719**	**5121**	**3280**	

* Newly completed studies (since original submission of NDA)
** Newly completed studies (since resubmission)
*** Excluded from analysis (no valid comparator; neither 20 mg or control)

2.2 STATISTICAL METHODOLOGY

The purpose of the statistical analysis is to estimate the effects of rimonabant vs. placebo on safety outcomes; therefore, nominal p values are presented without multiple comparison adjustment. The primary treatment group comparison was rimonabant 20 mg vs. placebo, stratified by study.

The studies included were randomized phase 2 and phase 3 trials. The sample sizes ranged from 20 to 3,000 per group. The study populations were diverse: alcoholics, obese (binge eating disorder, craving, diabetes, hyperlipidemia), schizophrenia, and smokers. A few studies had unbalanced randomizations (e.g. 2:1). In order to maintain the individual study randomizations and not combine data with unequal group sizes and from diverse populations, the stratified generalized Fisher's exact test (stratified by study and meta-analysis (combining estimates from individual studies) were performed. The less conservative mid- p adjusted confidence intervals were reported.

The primary safety outcome is suicidality. The secondary safety outcomes are psychiatric AE, neurological AE, and seizure.

For safety outcomes with relatively rare events (seizure and suicidality) the 'exact' test was performed as well as a fixed-effects meta-analysis. Exact tests were applied to both the incidence (number of patients) data and patient-year data. The exact test was performed using StatXact software.

For meta analyses of psychiatric and neurological AEs, I presented results for both fixed and random effects models. The random effects model considers the studies in the analysis as a random sample from a population of all possible studies, whereas the fixed effects model assumes the studies being analyzed are homogeneous in design and outcome.

The fixed effects model assumes the effect sizes are homogenous while the random effects model assumes the effect size varies from study to study. For the random effects model the inter-study variability is assumed and factored into the analysis. The homogeneity test for study-by-effect size interaction is presented; an alpha level of less than 0.1 indicates that the results are not homogeneous. In the fixed effects model, studies might not be considered combinable if the p value for homogeneity is significant. The weights for combining the

studies were computed as inverses of the study variances. The fixed effects model used a Mantel-Haenszel approach, and the random effects model was evaluated using DerSimonian Laird (DSL). However, the DSL method is not recommended for outcomes with relatively low event rates because the inverse weighing of within trial variance is imprecise. The meta-analysis results were displayed using forest plots from R software.

Risk ratio (RR), risk difference (RD), and odds ratio (OR) are all useful estimates in the statistical analysis of risk. The OR and RR are similar when the proportion of events is small for both groups. The OR and RR equal 0 (no placebo events) or ∞ (no rimonabant events) if all events occur in only one of the 2 treatment groups, and are undefined if both treatment groups have zero events. In order to calculate an estimated RR or OR, 0.5 was added to each cell of the 2x2 table when a zero was encountered. One advantage of RD is that even studies with no events in either treatment group can be included in the analysis.

In order to keep the randomization intact within each study, data from only the 1st randomization were included in the primary analysis. For study EFC4743, the first randomization assigned patients 2:1 to 20 mg rimonabant and placebo (1219:607). The 1st year completion rate was approximately ½. The re-randomization assigned 1st year 20 mg rimonabant patients 1:1 to 20 mg rimonabant and placebo. The 20 mg/20 mg rimonabant exposure (n=333) was 27% that of the first year (n=1219), while the placebo/placebo sample size was 49% of the first randomization (298/607). For study EFC4796, the 2nd randomization assigned patients who were compliant with treatment and abstinent from smoking after treatment with rimonabant and the sample size was approximately 30% of the first randomization. Sensitivity analyses were conducted that included the additional events from second randomizations.

2.3 SUICIDALITY

Data set PSRAE (Possibly Suicide-Related Adverse Events) classified events into 9 codes: 1. completed suicide, 2. suicide attempt, 3. preparatory acts toward imminent suicidal behavior, 4. suicidal ideation, 5. self-injurious behavior, 6. intent unknown, 7. self-injurious behavior, no suicidal intent, 8. other: accident; psychiatric; medical and 9. not enough information (nonfatal). Five of the 9 codes were present in the suicidality dataset (2, 3, 4, 6 and 9).

Table 5 displays the incidence rates and person-year rates for suicidality by study. Study ACT3801 was not included in the analysis for OR. Fourteen studies contributed to the analysis which had a total of 74 suicidality cases (1st randomization): 20 in placebo, 8 in 5 mg rimonabant and 46 in 20 mg rimonabant. Study ACT4389 which had no 20 mg rimonabant treatment group (1 case for placebo) and study EFC4798 which had no placebo treatment group (at 1st randomization) (1 case for 20 mg rimonabant) were excluded from the analysis. Studies EFC4743 and EFC4796 re-randomized patients during a maintenance phase treatment after the first randomized treatment. Only data from the first randomization were used in the meta-analysis. For asymptotic analyses, 0.5 was added to each of the four cells (2x2 table of 20 mg rimonabant vs. placebo) if either of the 2 treatments had zero events (5 studies). ***The control group for study EFC4796 was 5 mg rimonabant (as there was no placebo group).***

Table 5 Suicidality incidence and person-year rates – updated for all completed studies

		Incidence			Person-year		
		20 mg	5 mg	Placebo	20 mg	5 mg	Placebo
Population	Study	n/N (%)	n/N (%)	n/N (%)	n/person -year* (rate)	n/person-year* (rate)	n/person-year* (rate)
Alcoholics	ACT4855	3/131 (2.29%)		3/127 (2.36%)	3/26.2 (11.45)		3/23.5 (12.77)
Schizophrenia	METATR	7/72 (9.72%)		7/98 (7.14%)	7/4 (175)		7/5.6 (125)
Obese	DRI3388	1/69 (1.45%)	0/67	0/73	1/18.6 (5.38)	0/17.1	0/16.5
Obese (Eu)	EFC4733	6/599 (1%)	0/603	1/305 (0.33%)	6/761.8 (0.79)	0/794.5	1/377.8 (0.26)
Obese(Lipid)	EFC4735	3/346 (0.87%)	2/345 (0.58%)	2/342 (0.58%)	3/266.8 (1.12)	2/262.3 (0.76)	2/268.2 (0.75)
Obese(Diab)	EFC4736	2/339 (0.59%)	0/358	0/348	2/269.4 (0.74)	0/283.6	0/277.7
Obese (N.A.)	EFC4743**	7/1219 (0.57%)	4/1214 (0.33%)	4/607 (0.66%)	7/867.4 (0.81)	4/837.1 (0.48)	4/415.1 (0.96)
Obese (Crav)	EFC5031	1/76 (1.32%)		0/80	1/16.5 (6.06)		0/18.1
Obese (Diab)	EFC5825	1/138 (0.72%)		0/140	1/59.6 (1.68)		0/63.9
Obese (Crav)	ACT3801	0/143		0/146	0/57.9		0/59.9
Smokers	ACT4389			1/183 (0.55%)			1/28.6 (3.5)
Smokers	EFC4474	2/267 (0.75%)	1/256 (0.39%)	1/260 (0.38%)	2/41.5 (4.82)	1/39.6 (2.53)	1/41.1 (2.43)
Smokers	EFC4796**	12/3023 (0.40%)	0/2016		12/460.1 (2.61)	0/311.2	
Smokers	EFC4798	1/754 (0.13%)			1/109.1 (0.92)		
Smokers	EFC4964	0/261	1/262 (0.38%)	1/261 (0.38%)	0/43	1/42.3 (2.36)	1/42.9 (2.33)
Smokers	EFC5794	1/262 (0.38%)		1/268 (0.37%)	1/42 (2.38)		1/43.8 (2.28)

* per 100 person-years
** 1st randomization only

Table 6 displays the stratified test results for all studies and by patient population. P-values for the homogeneity test are displayed if they were significant. The homogeneity test was not significant for the obese population, whereas it was significant for smokers. The estimates are more consistent across the studies of obese patients than the studies of smokers.

Compared to placebo, 20 mg rimonabant statistically significantly increased suicidality based on analyses both of incidence rates and person-years.

Table 6 Suicidality Incidence and person-year rates: Rimonabant 20 mg versus placebo

	Overall 13 studies	Obese 7 studies	Smoker 4 studies	Schizophrenia 1 study	Alcoholics 1 study
Incidence					
Homogeneity	ns	ns	p=0.05	na	na
Exact OR	2.0 (1.2, 3.4) p=0.015	2.0 (0.9, 5.1) p=0.12	3.9 (1.2, 16.8) p=0.03	1.4 (0.4, 4.4) p=0.58	0.97 (0.2 5.7) p=1.0
Person-year					
Homogeneity	ns	ns	p=0.05	na	na
Exact RR	1.93 (1.1, 3.4)	1.95 (0.84, 4.99)	3.91 (1.22, 16.96)	1.40 (0.47, 4.17)	0.90 (0.15, 5.22)

Overall	Obese	Smoker	Schizophrenia	Alcoholics
13 studies	7 studies	4 studies	1 study	1 study
P=0.011	p=0.11	p=0.021	p=0.59	p=1.0

Table 7 and Figure 1 display the fixed effects meta-analysis results of 20 mg rimonabant vs. placebo for incidence rates of suicidality. The study ORs were sorted in descending order by treatment indication. The modified combined ORs were calculated by adding ½ events to each of the 2x2 table when one of the 2 treatment groups had no events. The placebo had no events in 5 of the 13 studies (obesity) and one study had no events in the 20 mg rimonabant group (smoking). For relatively rare events, the OR will be underestimated when the placebo treatment group has 0 events as happened here and also in studies with unbalanced randomizations. The overall fixed OR for the incidence of suicidality in the rimonabant 20 mg vs. placebo is underestimated as compared to the exact OR. The combined OR [95% CL] was 1.9 [1.1, 3.1]. Study EFC4796 (smoking) had the largest number of events in the rimonabant 20 mg group and the largest OR=16.7. The studies with 0 events in either one of the treatment groups had less weight in the analysis relative to the other studies. The relatively small Schizophrenia and Alcoholic studies, on the other hand, had greater event rates and were weighted relatively more than other studies. Studies with 0 cells will have large variances and, therefore, small weights (last column).

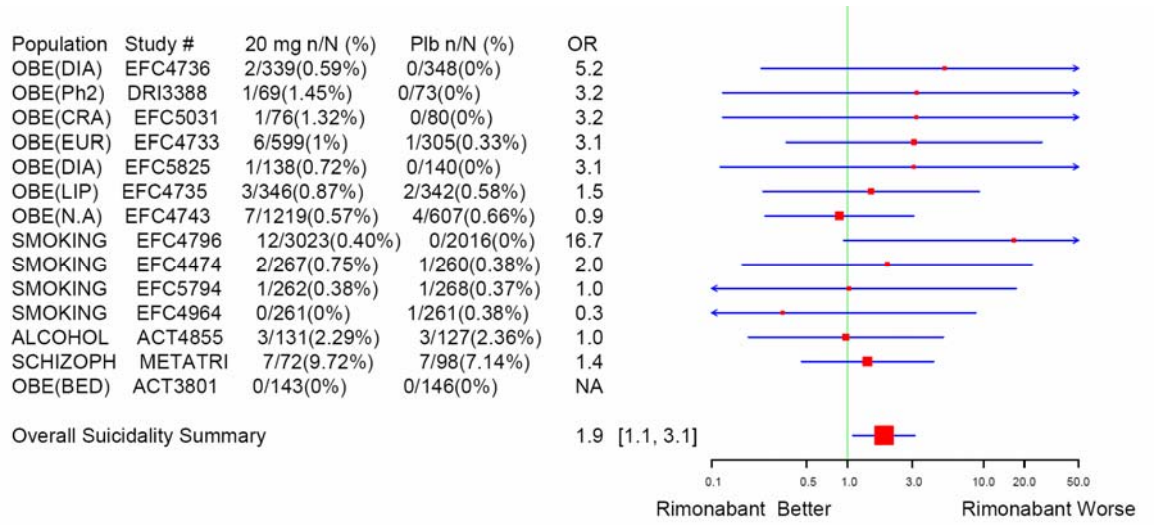
Table 7 Suicidality odds ratio for incidence: Rimonabant 20 mg versus placebo – 13 studies

Study Population	20 mg n/N (%)	Placebo n/N (%)	OR	95%, lower	CI upper	Fixed Wt %
OBE(DIA) EFC4736	2/339 (0.59%)	0/348 (0%)	5.16	0.25	107.94	2.1
OBE(Ph2) DRI3388	1/69 (1.45%)	0/73 (0%)	3.22	0.13	80.36	2.1
OBE(CRA) EFC5031	1/76 (1.32%)	0/80 (0%)	3.20	0.13	79.74	2.1
OBE(EUR) EFC4733	6/599 (1%)	1/305 (0.33%)	3.08	0.37	25.66	5.7
OBE(DIA) EFC5825	1/138 (0.72%)	0/140 (0%)	3.07	0.12	75.90	2.1
OBE(LIP) EFC4735	3/346 (0.87%)	2/342 (0.58%)	1.49	0.25	8.95	8.7
OBE(N.A) EFC4743	7/1219 (0.57%)	4/607 (0.66%)	0.87	0.25	2.99	23.1
SMOKING EFC4796	12/3023 (0.40%)	0/2016 (0%)*	16.74	0.99	282.89	2.6
SMOKING EFC4474	2/267 (0.75%)	1/260 (0.38%)	1.95	0.18	21.69	4.4
SMOKING EFC5794	1/262 (0.38%)	1/268 (0.37%)	1.02	0.06	16.44	4.3
SMOKING EFC4964	0/261 (0%)	1/261 (0.38%)	0.33	0.01	8.19	6.5
ALCOHOL ACT4855	3/131 (2.29%)	3/127 (2.36%)	0.97	0.19	4.89	13.0
SCHIZOPH METATRI	7/72 (9.72%)	7/98 (7.14%)	1.40	0.47	4.18	23.3
Overall Fixed			1.85	(1.11	3.10)	p=0.0184

Test of homogeneity p=0.86

* The control group for study EFC4796 was rimonabant 5 mg

Figure 1 Odds Ratio for incidence of suicidality: 20 mg rimonabant vs. placebo



Sensitivity analysis

The sponsor indicated that "As an exact date was not always available for 'suicidality' reported as an associated symptom, all events were displayed according to the first treatment received (whatever the re-randomization)." The sensitivity analysis includes all suicidality events ignoring re-randomization using the first randomization patient number as the sample size. Compared to the primary analysis in study EFC4743, 2 more events were added to the placebo group and one more event added to the 20 mg rimonabant group (20 mg/plb). There were 4 additional events in study EFC4796, 3 events for 20 mg rimonabant (2 20mg/20mg and 1 20mg/5mg) and 1 for 5mg/5mg group. The exact test OR [95% CL] was 1.71 [1.04, 2.86]. The p value was 0.04. The homogeneity test was not significant (p=0.50). Table 8 and Figure 2 display the meta-analysis results using the fixed effects model which is similar to the exact test results.

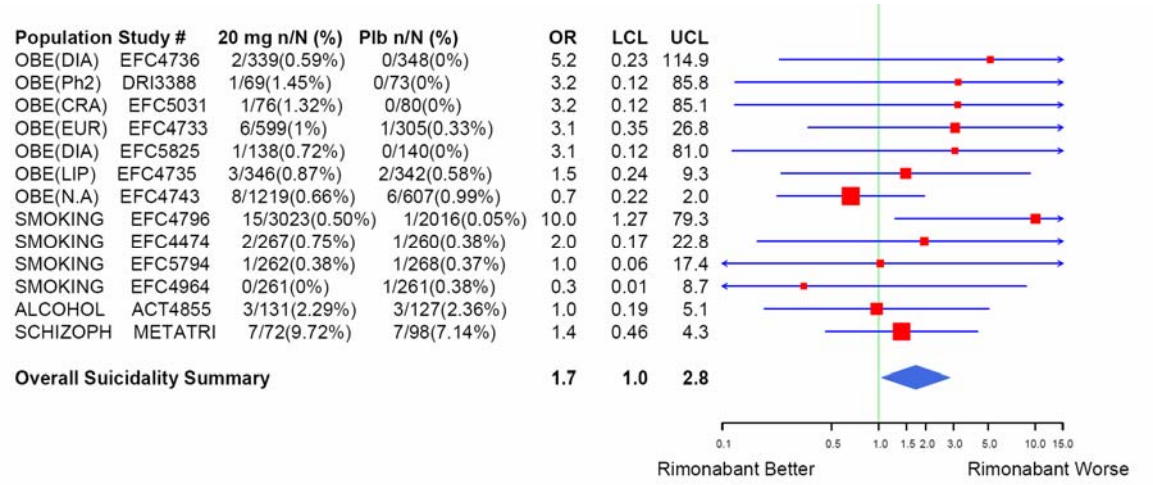
Table 8 Suicidality odds ratio for incidence: Rimonabant 20 mg versus placebo – Sensitivity analysis

Study Population	20 mg n/N (%)	Placebo n/N (%)	OR	95%, CI lower	CI upper	Fixed Wt
OBE(DIA) EFC4736	2/339(0.59%)	0/348(0%)	5.16	0.25	107.94	1.9
OBE(Ph2) DRI3388	1/69(1.45%)	0/73(0%)	3.22	0.13	80.36	1.8
OBE(CRA) EFC5031	1/76(1.32%)	0/80(0%)	3.20	0.13	79.74	1.8
OBE(EUR) EFC4733	6/599(1%)	1/305(0.33%)	3.08	0.37	25.66	5.0
OBE(DIA) EFC5825	1/138(0.72%)	0/140(0%)	3.07	0.12	75.90	1.9
OBE(LIP) EFC4735	3/346(0.87%)	2/342(0.58%)	1.49	0.25	8.95	7.6
OBE(N.A) EFC4743	8/1219(0.66%)	6/607(0.99%)	0.66	0.23	1.92	30.4
SMOKING EFC4796	15/3023(0.50%)	1/2016(0.05%)	10.05	1.33	76.13	4.6
SMOKING EFC4474	2/267(0.75%)	1/260(0.38%)	1.95	0.18	21.69	3.8
SMOKING EFC5794	1/262(0.38%)	1/268(0.37%)	1.02	0.06	16.44	3.8
SMOKING EFC4964	0/261(0%)	1/261(0.38%)	0.33	0.01	8.19	5.7
ALCOHOL ACT4855	3/131(2.29%)	3/127(2.36%)	0.97	0.19	4.89	11.4

Study Population	20 mg n/N (%)	Placebo n/N (%)	OR	95%, lower	CI upper	Fixed Wt
SCHIZOPH METATRI	7/72(9.72%)	7/98(7.14%)	1.40	0.47	4.18	20.4
Overall Fixed			1.72	(1.06	2.81)	p=0.0283

Test of homogeneity p=0.70

Figure 2 Odds Ratio for incidence of suicidality: 20 mg rimonabant vs. placebo sensitivity analysis (ignoring 2nd randomization)



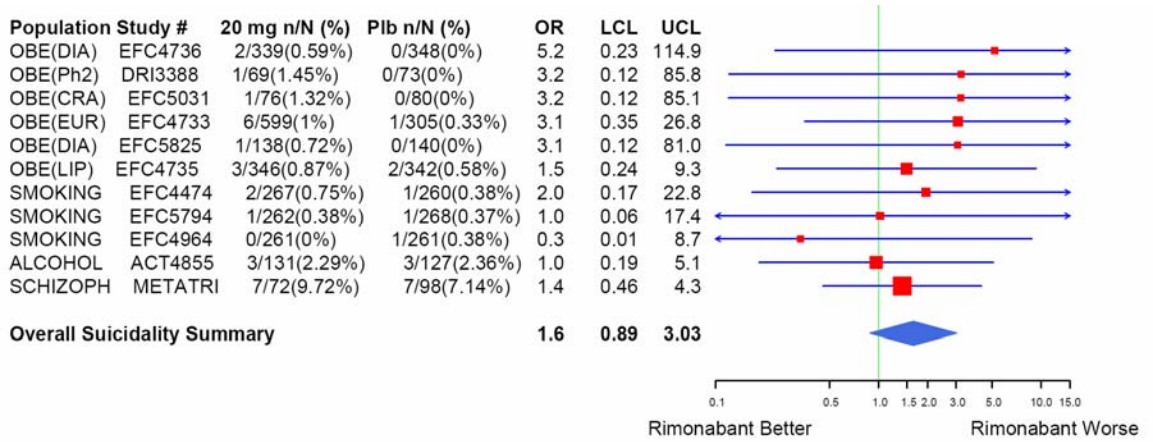
If the 2 largest re-randomized studies were excluded, the OR [95% CL] from exact test was 1.72 [0.88, 3.49]. The p value was 0.12. The homogeneity test was not significant (p=0.83). Table 9 and figure 3 display the fixed effects model result of the meta-analysis without these 2 studies. The OR [95% CL] was 1.64 [0.90, 2.99]. The p value was 0.11. The homogeneity test was not significant (p=0.98). The Schizophrenia metatrial contributed the largest weight (approximately 30%).

Table 9 Suicidality odds ratio for incidence: Rimonabant 20 mg versus placebo – Sensitivity analysis using 11 studies

Study Population	20 mg n/N (%)	Placebo n/N (%)	OR	95%, lower	CI upper	Fixed % Wt
OBE(DIA) EFC4736	2/339(0.59%)	0/348(0%)	5.16	0.25	107.94	2.9
OBE(Ph2) DRI3388	1/69(1.45%)	0/73(0%)	3.22	0.13	80.36	2.8
OBE(CRA) EFC5031	1/76(1.32%)	0/80(0%)	3.20	0.13	79.74	2.8
OBE(EUR) EFC4733	6/599(1%)	1/305(0.33%)	3.08	0.37	25.66	7.7
OBE(DIA) EFC5825	1/138(0.72%)	0/140(0%)	3.07	0.12	75.90	2.9
OBE(LIP) EFC4735	3/346(0.87%)	2/342(0.58%)	1.49	0.25	8.95	11.7
SMOKING EFC4474	2/267(0.75%)	1/260(0.38%)	1.95	0.18	21.69	5.9
SMOKING EFC5794	1/262(0.38%)	1/268(0.37%)	1.02	0.06	16.44	5.8
SMOKING EFC4964	0/261(0%)	1/261(0.38%)	0.33	0.01	8.19	8.8
ALCOHOL ACT4855	3/131(2.29%)	3/127(2.36%)	0.97	0.19	4.89	17.5
SCHIZOPH METATRI	7/72(9.72%)	7/98(7.14%)	1.40	0.47	4.18	31.4
Overall Fixed			1.64	(0.90	2.99)	p=0.1077

Test of homogeneity p=0.98

Figure 3 Odds Ratio for incidence of suicidality: 20 mg rimonabant vs. placebo sensitivity analysis (excluding studies with 2nd randomization)



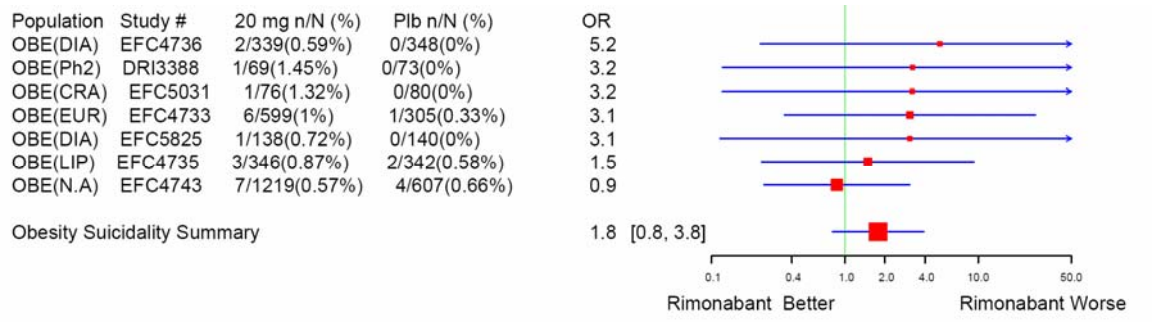
For the 7 obesity studies, the p-value for homogeneity was not significant (p=0.88). Meta-analysis results are presented in Table 10 and Figure 4. The exact test OR [95% CL] was 2.00 [0.86, 5.10]. The p value was 0.12.

Table 10 Suicidality OR for incidence: Rimonabant 20 mg versus placebo – 7 obesity studies

Study Population	20 mg n/N (%)	Placebo n/N (%)	OR	95%, lower	CI upper	Fixed Wt
OBE(DIA) EFC4736	2/339(0.59%)	0/348(0%)	5.16	0.25	107.94	4.6
OBE(Ph2) DRI3388	1/69(1.45%)	0/73(0%)	3.22	0.13	80.36	4.5
OBE(CRA) EFC5031	1/76(1.32%)	0/80(0%)	3.20	0.13	79.74	4.5
OBE(EUR) EFC4733	6/599(1%)	1/305(0.33%)	3.08	0.37	25.66	12.4
OBE(DIA) EFC5825	1/138(0.72%)	0/140(0%)	3.07	0.12	75.90	4.7
OBE(LIP) EFC4735	3/346(0.87%)	2/342(0.58%)	1.49	0.25	8.95	18.9
OBE(N.A) EFC4743	7/1219(0.57%)	4/607(0.66%)	0.87	0.25	2.99	50.3
Overall Fixed			1.77	[0.82,	3.84]	p=0.145

Test of homogeneity p=0.88

Figure 4 Odds Ratio of suicidality 20 mg rimonabant vs. placebo – 7 Obesity studies



For sensitivity analysis, the 2nd randomization events were added to the 1st randomization. The exact test OR [95% CL] was 1.93 [0.92, 4.28]. The p value was 0.11. Table 11 and Figure

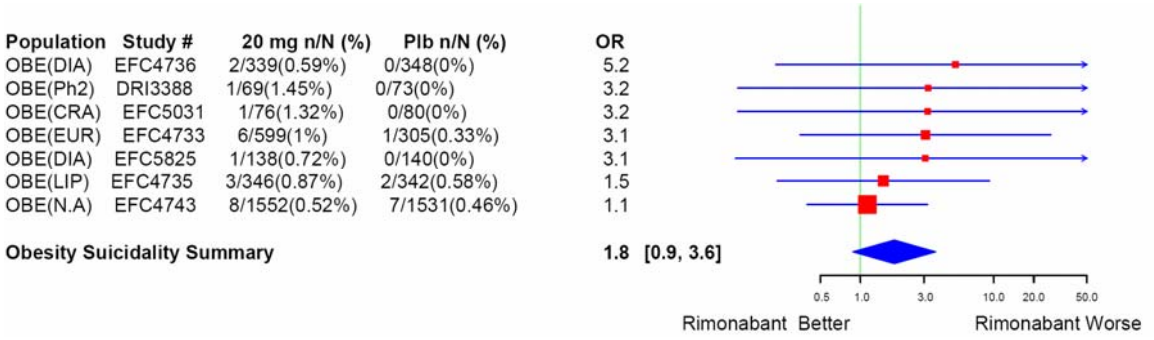
5 display the meta-analysis results. The OR [95% CL] was 1.80 [0.89, 3.63]. The p value was 0.103.

Table 11 Suicidality OR for incidence: Rimonabant 20 mg versus placebo – 7 obesity studies, Sensitivity analysis

Study Population	20 mg n/N (%)	Placebo n/N (%)	OR	95%, lower	CI upper	Fixed Wt
OBE(DIA) EFC4736	2/339(0.59%)	0/348(0%)	5.16	0.25	107.94	4.0
OBE(Ph2) DRI3388	1/69(1.45%)	0/73(0%)	3.22	0.13	80.36	3.9
OBE(CRA) EFC5031	1/76(1.32%)	0/80(0%)	3.20	0.13	79.74	3.9
OBE(EUR) EFC4733	6/599(1%)	1/305(0.33%)	3.08	0.37	25.66	10.7
OBE(DIA) EFC5825	1/138(0.72%)	0/140(0%)	3.07	0.12	75.90	4.0
OBE(LIP) EFC4735	3/346(0.87%)	2/342(0.58%)	1.49	0.25	8.95	16.3
OBE(N.A) EFC4743	8/1552(0.52%)	7/1531(0.46%)	1.13	0.41	3.12	57.2
Overall Fixed			1.80	[0.89,	3.63]	p=0.103

Test of homogeneity p=0.93

Figure 5 Odds Ratio of suicidality 20 mg rimonabant vs. placebo – 7 Obesity studies



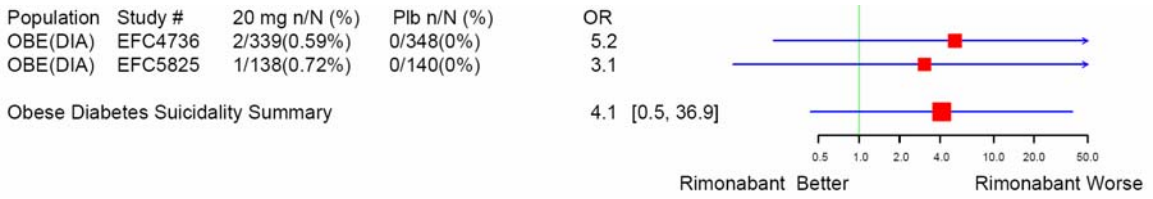
For the 2 obesity diabetes studies, the exact test had infinite OR (no placebo events). Table 12 and Figure 6 display the meta-analysis results. The OR [95% CL] was 4.1 [0.5, 36.9]. The p value was 0.21.

Table 12 Suicidality OR for incidence: Rimonabant 20 mg versus placebo – 2 obese diabetes studies,

Study Population	20 mg n/N (%)	Placebo n/N (%)	OR	95%, lower	CI upper	Fixed Wt	Rand Wt
OBE(DIA) EFC4736	2/339(0.59%)	0/348(0%)	5.16	0.25	107.94	50%	53%
OBE(DIA) EFC5825	1/138(0.72%)	0/140(0%)	3.07	0.12	75.90	50%	47%
Overall Fixed			4.11	0.46,	36.9]		p=0.207

H: p=0.82

Figure 6 Odds Ratio of suicidality 20 mg rimonabant vs. placebo – 2 Obese diabetes studies



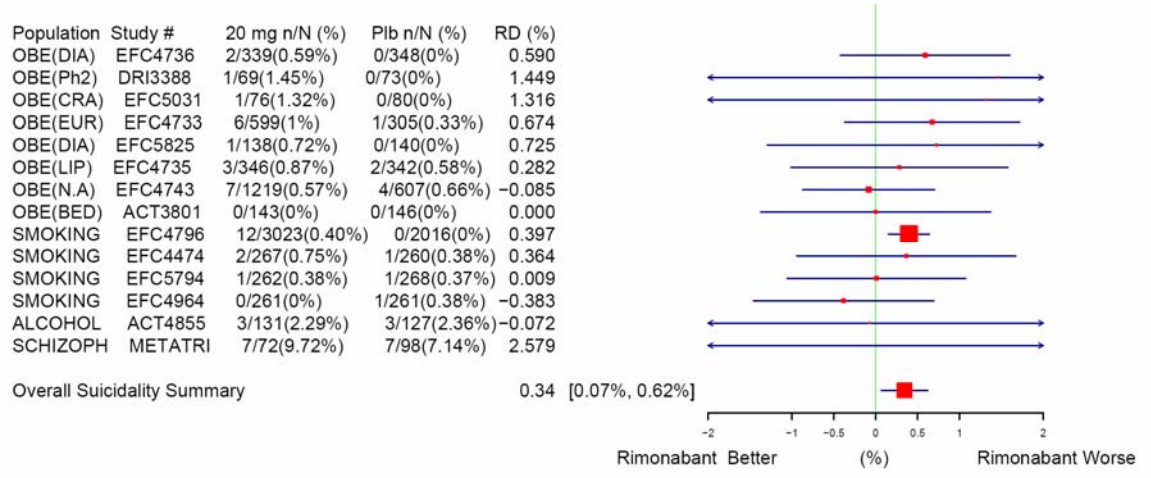
A total of 14 studies contributed to the risk difference analysis which included study ACT3801 that had no events. The common risk difference estimate of suicidality was 0.34% with a 95% confidence interval of 0.07% to 0.62% (Table 13 and Figure 7). The p-value was significant (0.014). The homogeneity test was not significant (p=0.96). As shown in Table 13, study EFC4796 had the greatest weighting in the analysis (last column).

Table 13 Suicidality risk differences: Rimonabant 20 mg versus placebo – 14 studies

Study Population	20 mg n/N (%)	Placebo n/N (%)	RD	95%, lower	CI upper	Fixed % Wt
OBE(DIA) EFC4736	2/339 (0.59%)	0/348 (0%)	0.59%	-0.40%	1.58%	5.97
OBE(Ph2) DRI3388	1/69 (1.45%)	0/73 (0%)	1.45%	-2.42%	5.32%	1.23
OBE(CRA) EFC5031	1/76 (1.32%)	0/80 (0%)	1.32%	-2.21%	4.84%	1.35
OBE(EUR) EFC4733	6/599 (1%)	1/305 (0.33%)	0.67%	-0.35%	1.70%	7.02
OBE(DIA) EFC5825	1/138 (0.72%)	0/140 (0%)	0.72%	-1.25%	2.70%	2.42
OBE(LIP) EFC4735	3/346 (0.87%)	2/342 (0.58%)	0.28%	-0.99%	1.55%	5.98
OBE(N.A) EFC4743	7/1219 (0.57%)	4/607 (0.66%)	-0.08%	-0.86%	0.69%	14.08
OBE(BED) ACT3801	0/143	0/146	0.00%	-1.34%	1.34%	2.51
SMOKING EFC4796	12/3023 (0.40%)	0/2016 (0%)	0.40%	0.16%	0.64%	42.03
SMOKING EFC4474	2/267 (0.75%)	1/260 (0.38%)	0.36%	-0.91%	1.64%	4.58
SMOKING EFC5794	1/262 (0.38%)	1/268 (0.37%)	0.01%	-1.04%	1.05%	4.6
SMOKING EFC4964	0/261 (0%)	1/261 (0.38%)	-0.38%	-1.44%	0.67%	4.54
ALCOHOL ACT4855	3/131 (2.29%)	3/127 (2.36%)	-0.07%	-3.75%	3.61%	2.24
SCHIZOPH METATRI	7/72 (9.72%)	7/98 (7.14%)	2.58%	-5.95%	11.11%	1.44
Overall Fixed			0.34%	(0.07%	0.62%)	p=0.0138

Test of homogeneity p=0.96

Figure 7 Risk differences of suicidality 20 mg rimonabant vs. placebo – 14 studies



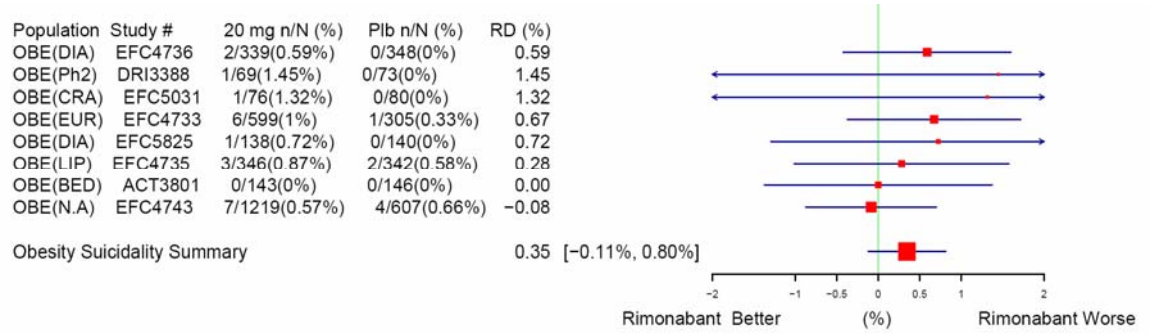
For the 8 obesity studies, the risk difference [95% CI] was 0.32% [-0.12%, 0.76%]. The p-value was 0.14 (Table 14 and Figure 8).

Table 14 Suicidality risk differences: Rimonabant 20 mg versus placebo – 8 obesity studies

Study Population	20 mg n/N (%)	Placebo n/N (%)	RD	95%, lower	CI upper	Fixed % Wt
OBE(DIA) EFC4736	2/339 (0.59%)	0/348 (0%)	0.59%	-0.40%	1.58%	14.71
OBE(Ph2) DRI3388	1/69 (1.45%)	0/73 (0%)	1.45%	-2.42%	5.32%	3.04
OBE(CRA) EFC5031	1/76 (1.32%)	0/80 (0%)	1.32%	-2.21%	4.84%	3.34
OBE(EUR) EFC4733	6/599 (1%)	1/305 (0.33%)	0.67%	-0.35%	1.70%	17.31
OBE(DIA) EFC5825	1/138 (0.72%)	0/140 (0%)	0.72%	-1.25%	2.70%	5.95
OBE(LIP) EFC4735	3/346 (0.87%)	2/342 (0.58%)	0.28%	-0.99%	1.55%	14.74
OBE(BED) ACT3801	0/143	0/146	0.00%	-1.34%	1.34%	6.19
OBE(N.A) EFC4743	7/1219 (0.57%)	4/607 (0.66%)	-0.08%	-0.86%	0.69%	34.72
Overall Fixed			0.34%	(-0.11%	0.80%)	p=0.14

Test of homogeneity p=0.90

Figure 8 Risk differences of suicidality 20 mg rimonabant vs. placebo –8 obesity studies



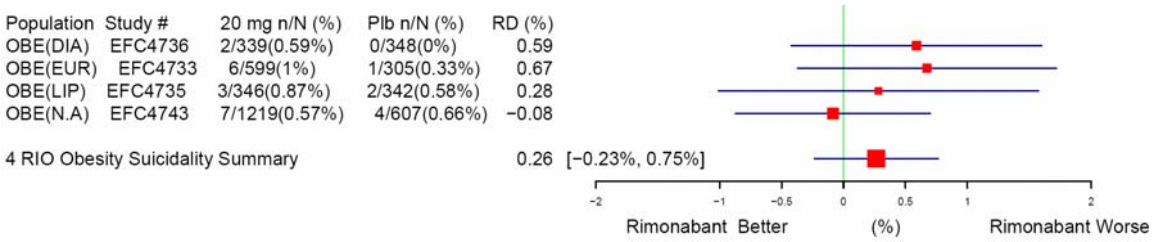
The RD [95% CL] for the 4 RIO studies was 0.26% [-0.23%, 0.75%] (Table 15 & Fig 9). The p value was 0.29.

Table 15 Suicidality risk differences: Rimonabant 20 mg versus placebo for 7 obesity studies

Study Population	20 mg n/N (%)	Placebo n/N (%)	RD	95%, lower	CI upper	Fixed Wt
OBE(DIA) EFC4736	2/339 (0.59%)	0/348 (0%)	0.59%	-0.40%	1.58%	18.06
OBE(EUR) EFC4733	6/599 (1%)	1/305 (0.33%)	0.67%	-0.35%	1.70%	21.25
OBE(LIP) EFC4735	3/346 (0.87%)	2/342 (0.58%)	0.28%	-0.99%	1.55%	18.09
OBE(N.A) EFC4743	7/1219 (0.57%)	4/607 (0.66%)	-0.08%	-0.86%	0.69%	42.61
Overall Fixed			0.26%	(-0.23%	0.75%)	p=0.29

Test of homogeneity p=0.61

Figure 9 Risk differences of suicidality 20 mg rimonabant vs. placebo – 4 RIO studies



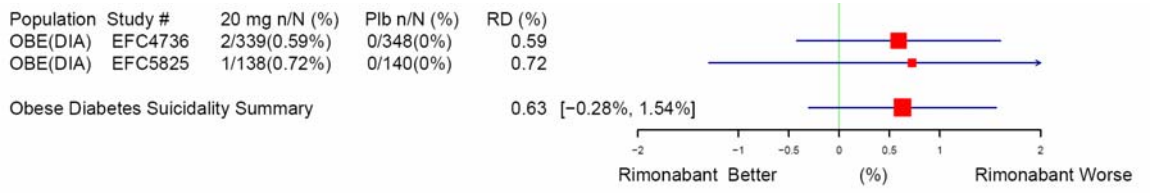
For the 2 obese diabetes studies the RD was highest at 0.63%. The 95% CL were [-0.28%, 1.54%]. The p value was 0.18 (Table 16 and Fig 10).

Table 16 Suicidality risk differences: Rimonabant 20 mg versus placebo – 2 obese diabetes studies

Study Population	20 mg n/N (%)	Placebo n/N (%)	RD	95%, lower	CI upper	Fixed % Wt
OBE(DIA) EFC4736	2/339 (0.59%)	0/348 (0%)	0.59%	-0.40%	1.58%	71.2
OBE(DIA) EFC5825	1/138 (0.72%)	0/140 (0%)	0.72%	-1.25%	2.70%	28.8
Overall Fixed			0.63%	(-0.28%	1.54%)	p=0.18

Test of homogeneity p=0.90

Figure 10 Risk differences of suicidality 20 mg rimonabant vs. placebo – 2 obese diabetes studies



2.4 PSYCHIATRIC AE

Table 17 displays the percentage of patients with at least one psychiatric TEAE for the 13 Phase 3 studies. All patients in Study EFC4798 for smoking cessation were treated with rimonabant 20 mg (plus nicotine patch 21 mg daily or plus placebo patch). Studies without a comparator group were not included in the meta-analysis. For Study EFC4796 (maintenance of smoking abstinence), 20 mg rimonabant was compared to 5 mg rimonabant. Data from the first randomization for Studies EFC4743 (obesity) and EFC4796 (smoking cessation) were used in the analysis. In the table and graphs, the relative risks (RR) of rimonabant 20 mg vs. placebo are sorted in descending order. In all studies, the percent of patients with at least one TEAE was greater in the rimonabant group than the placebo group.

Table 17 Percentage of patients with at least 1 psychiatric TEAE

#	Study	Population	20 mg rimonabant	5 mg rimonabant	Placebo
1	EFC5031	OBE, CRV	16/76 (21%)		3/80 (4%)
2	EFC4735	OBE, LIP	95/346 (27%)	51/345 (15%)	38/342 (11%)
3	ACT3801	OBE, BED	39/143 (27%)		18/146 (12%)
4	EFC4736	OBE, DIA	84/339 (25%)	30/358 (8%)	41/348 (12%)
5	EFC4743*	OBE, N.A.	285/1219 (23%)	195/1214 (16%)	86/607 (14%)
6	EFC5825	OBE, DIA (Serenade)**	24/138 (17%)		15/140 (11%)
7	EFC4733	OBE, EU	163/599 (27%)	113/603 (19%)	54/305 (18%)
8	EFC5745	OBE, INS	3/20 (15%)		2/20 (10%)
9	EFC4474	SMK	97/267 (36%)	74/256 (29%)	64/260 (25%)
10	EFC4796*	SMK	788/3023 (26%)	377/2016 (19%)	
11	EFC4964	SMK	70/261 (27%)	46/262 (18%)	59/261 (23%)
12	EFC5794	SMK	48/262 (18%)		48/268 (18%)
13	EFC4798	SMK	185/754 (25%)		

* 1st randomization only

** updated after resubmission in February 2007

Table 18 displays the percentages of psychiatric AE during the 2nd randomization treatment for studies EFC4743 and EFC4796. Stratified by studies the RR [95% CL] was 1.64 [1.2, 2.3] for 20mg/20mg vs. plb/plb for EFC4796. For EFC4796 the 5mg/plb was the comparator. The RR was similar to the 1st randomization RR=1.6 [1.4, 1.9]. The p value was 0.0031. The homogeneity test was not significant (p=0.98).

Table 18 Percentage of patients with at least 1 psychiatric AE – 2nd randomization

STUDY	20mg/20mg	20mg/5mg	20mg/plb	5mg/5mg	5mg/plb	plb/plb	Fixed %W
EFC4743	36/333 (10.8%)	-	30/326 (9.2%)	29/300 (9.7%)	22/300 (7.3%)	20/298 (6.7%)	37
EFC4796	59/340 (17.4%)	51/335 (15.2%)	42/342 (12.3%)	39/322 (12.1%)	35/322 (10.9%)	-	63

Figure 11 Risk ratio of psychiatric AE for 20 mg rimonabant vs. comparator – 2nd randomization

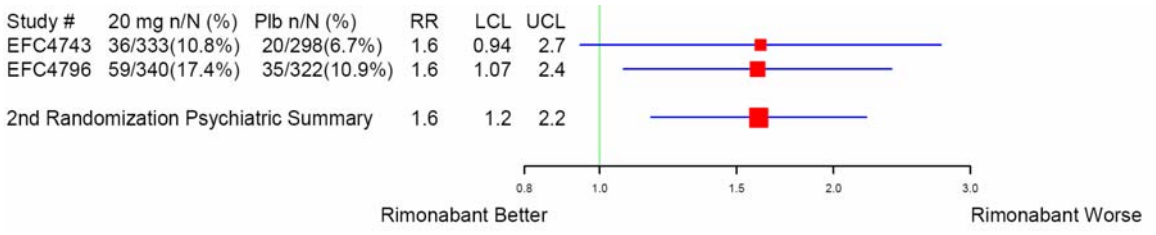


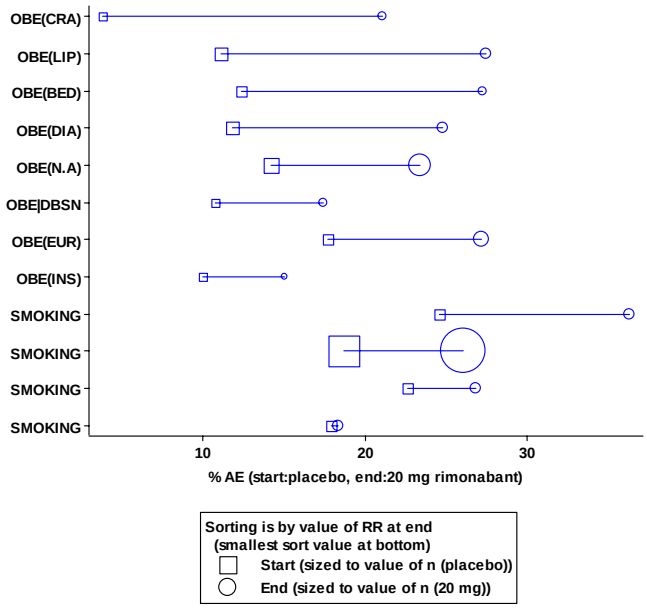
Table 19 displays the percentage of psychiatric AE in phase 2 studies. The 4 DFI studies in the table below were pooled as METATRIAL for suicidality analysis (schizophrenia population).

Table 19 Percentage of patients with at least 1 psychiatric TEAE – Phase 2 studies

STUDY	Rimonabant 40 mg	Rimonabant 20 mg	Rimonabant 10 mg	Rimonabant 5 mg	Placebo	Haloperidol 10 mg
ACT4389	65/183 (36%)	-	-	-	24/183 (13%)	-
ACT4855	-	19/131 (15%)	-	-	20/127 (16%)	-
DFI3024	-	-	-	-	9/25 (36%)	8/26 (31%)
DFI3067	-	-	-	-	8/22 (36%)	9/22 (41%)
DFI3077	-	22/72 (31%)	-	-	10/26 (38%)	7/25 (28%)
DFI3138	-	-	-	-	9/25 (36%)	12/25 (48%)
DRI3388	-	5/69 (7%)	6/68 (9%)	4/67 (6%)	2/73 (3%)	-
PDY3796	7/23 (30%)	-	-	-	1/22 (5%)	-

For phase 3 studies, Fig. 12 displays the percent of patients with ≥1 psychiatric TEAE for placebo (square) and 20 mg rimonabant (circle) sorted by relative risk (20 mg vs. placebo). In general, the obesity studies had a lower placebo rate and a greater risk difference than the studies in smokers.

Figure 12 Percent of patients with one or more psychiatric TEAe



The meta-analysis showed that risk ratios of all studies were ≥1 regardless of patient population. Furthermore, RRs for the obesity studies were greater than that of the smoking cessation studies (Table 20 & Figure 13).

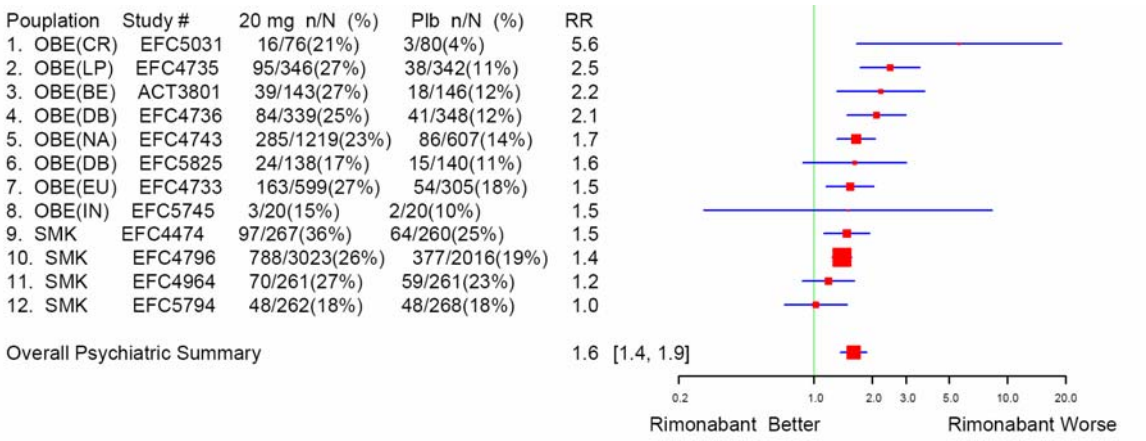
The stratified RR was 1.6 with a 95% confidence interval of 1.4 to 1.9. The relative risk was statistically significantly worse for the 20 mg rimonabant group than the placebo group (p<0.0001). The test for homogeneity was significant (p=0.0032).

Table 20 Meta-analysis of RR of 20 mg rimonabant vs. placebo – psychiatric AE

Study Population	20 mg n/N (%)	Placebo n/N (%)	RR	95%, upper	CI lower	Fixed %Wt	Rand %Wt
1. OBE(CR) EFC5031	16/76(21%)	3/80(4%)	5.6	(1.7	18.5)	0.3	1.5
2. OBE(LP) EFC4735	95/346(27%)	38/342(11%)	2.5	(1.7	3.5)	4.1	9.0
3. OBE(BE) ACT3801	39/143(27%)	18/146(12%)	2.2	(1.3	3.7)	1.9	5.8
4. OBE(DB) EFC4736	84/339(25%)	41/348(12%)	2.1	(1.5	3.0)	4.4	9.1
5. OBE(NA) EFC4743	285/1219(23%)	86/607(14%)	1.7	(1.3	2.1)	12.4	12.6
6. OBE(DB) EFC5825	24/138(17%)	15/140(11%)	1.6	(0.9	3.0)	1.6	4.6
7. OBE(EU) EFC4733	163/599(27%)	54/305(18%)	1.5	(1.2	2.0)	7.7	10.9
8. OBE(IN) EFC5745	3/20(15%)	2/20(10%)	1.5	(0.3	8.0)	0.2	0.8
9. SMK EFC4474	97/267(36%)	64/260(25%)	1.5	(1.1	1.9)	7.0	11.2
10. SMK EFC4796	788/3023(26%)	377/2016(19%)	1.4	(1.2	1.6)	48.8	15.8
11. SMK EFC4964	70/261(27%)	59/261(23%)	1.2	(0.9	1.6)	6.4	10.2
12. SMK EFC5794	48/262(18%)	48/268(18%)	1.0	(0.7	1.5)	5.1	8.6
Overall Fixed			1.52	(1.41,	1.64)		p<0.0001
Overall Random			1.60	(1.38,	1.86)		p<0.0001

Test for homogeneity: p=0.0032

Figure 13 RR *for incidence of psychiatric AE: 20 mg rimonabant vs. placebo -Phase 3 studies*

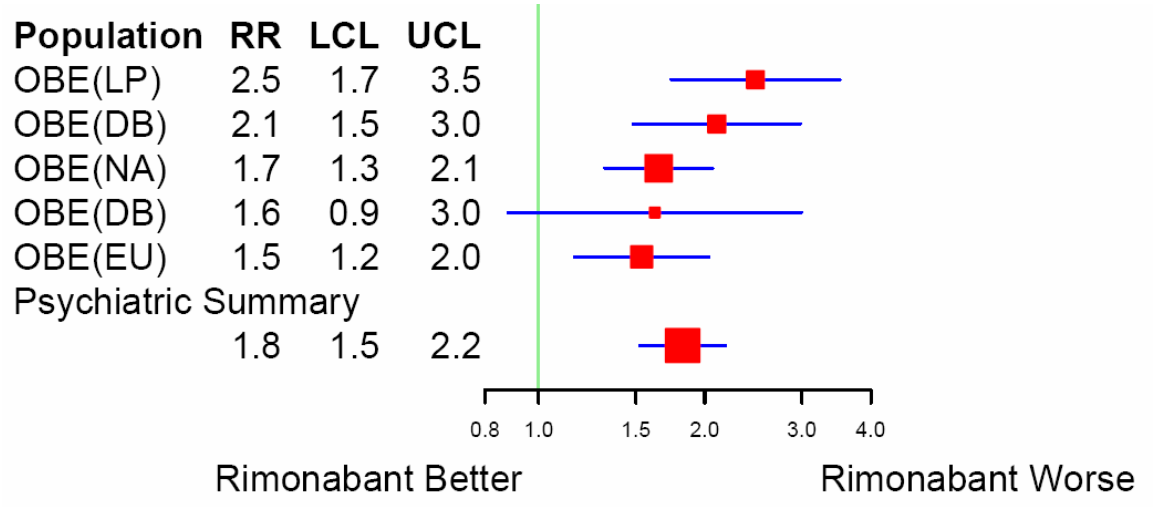


The combined RR for the 4 RIO and SERENADE (EFC5825) studies was 1.82 with a 95% CL of 1.53 to 2.17. The p value was highly significant (<0.0001) (Table 21 & Fig. 14).

Table 21 RR for incidence of psychiatric: 20 mg rimonabant vs. placebo – RIO+Serenade

Study	RR	95% CI			
		Lower	Upper	%W(fixed)	%W(random)
OBE(LP)	2.47	1.75	3.49	13.7	18.3
OBE(DB) EFC4736	2.10	1.49	2.96	14.5	18.5
OBE(NA)	1.65	1.32	2.06	41.0	31.2
OBE(DB) EFC5825	1.62	0.89	2.96	5.3	7.5
OBE(EU)	1.54	1.17	2.02	25.6	24.5
Fixed	1.80	1.57	2.06	p<0.0001	
Random	1.82	1.53	2.17	p<0.0001	
Homogeneity				p=0.20	

Figure 14 RR for incidence of psychiatric AE: 20 mg rimonabant vs. placebo – RIO+Serenade



For the 4 RIO obesity studies the RR [95% CL] was 1.85 [1.51, 2.27] (Table 22 & Fig. 15)

Table 22 RR for incidence of psychiatric: 20 mg rimonabant vs. placebo – RIO

Study	RR	95% CI			
		Lower	Upper	%W(fixed)	%W(random)
OBE(LP)	2.47	1.75	3.49	14	21
OBE(DB)	2.10	1.49	2.96	15	21
OBE(NA)	1.65	1.32	2.06	43	32
OBE(EU)	1.54	1.17	2.02	27	26
Fixed	1.81	1.57	2.08	p<0.0001	
Random	1.85	1.51	2.27	p<0.0001	
Homogeneity				p=0.12	

Figure 15 RR for incidence of psychiatric: 20 mg rimonabant vs. placebo – RIO

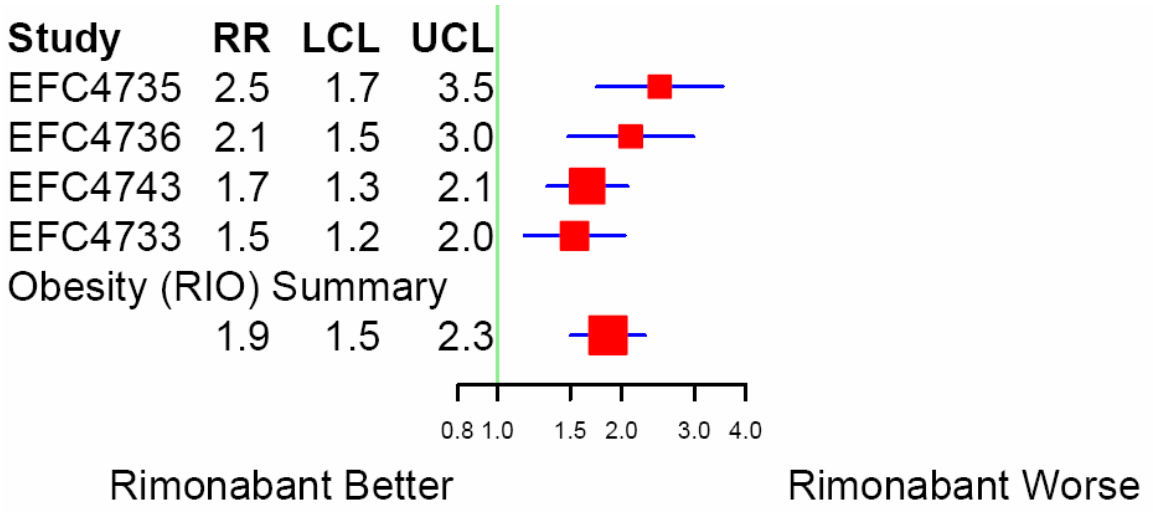
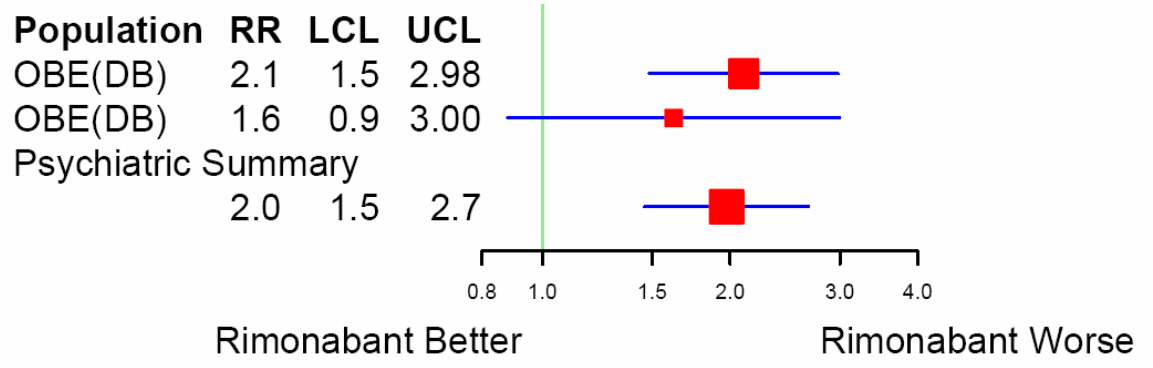


Table 23 and Figure 16 display the estimates for the 2 studies in obese diabetics (RIO DIABETES & SERENADE). The RR [95% CL] was 2.0 [1.47, 2.66].

Table 23 RR for incidence of psychiatric: 20 mg rimonabant vs. placebo – RIO

Study	RR	95% CI			
		Lower	Upper	%W(fixed)	%W(random)
EFC4736	2.10	1.49	2.96	73	76
EFC5825	1.62	0.89	2.96	27	24
Fixed	2.0	1.47	2.66	p<0.0001	
Random	2.0	1.47	2.66	p<0.0001	
Homogeneity				p=0.46	

Figure 16 RR for incidence of psychiatric: 20 mg rimonabant vs. placebo – 2 Studies in Obese Diabetics



2.5 NEUROLOGICAL AE

For an analysis neurological AEs, adverse events were identified in the database using the following terms:

> Amnesia, Balance Disorder, Burning Sensation, Carpal Tunnel Syndrome, Clonus, Clumsiness, Cognitive Disorder, Coordination Abnormal, Depressed Level Of Consciousness, Diabetic Neuropathy, Disturbance In Attention, Dysaesthesia, Facial Neuralgia, Facial Palsy, Formication, Hemiparesis, Hyperaesthesia, Hypoaesthesia, Lethargy, Loss Of Consciousness, Memory Impairment, Mental Impairment, Meralgia Paraesthetica, Motor Dysfunction, Neuropathy, Paraesthesia, Peroneal Nerve Palsy, Sedation, Sensory Disturbance, Somnolence, Syncope, Syncope Vasovagal, Tinel's Sign, Tremor, Ulnar Nerve Palsy.

The incidences of these neurological adverse events are summarized in Table 24 below.

Table 24 RR for incidence of neurological AE: 20 mg rimonabant vs. placebo

STUDY	Population	20 mg rimonabant n/N (%)	5 mg rimonabant n/N (%)	Placebo n/N (%)
EFC5825	OBE (DIA)	13/139 (9%)		4/141 (3%)
EFC4735	OBE (LIP)	38/346 (11%)	26/345 (8%)	15/342 (4%)
EFC4736	OBE (DIA)	37/339 (11%)	21/358 (6%)	13/348 (4%)
EFC4743	OBE (N.A)	93/1219 (8%)	65/1214 (5%)	35/607 (6%)
EFC5031	OBE (CRA)	3/76 (4%)		2/80 (3%)
ACT3801	OBE (BED)	5/143 (3%)		4/146 (3%)
EFC4733	OBE (EUR)	43/599 (7%)	34/603 (6%)	21/305 (7%)
EFC5745	OBE (INS)	1/20 (5%)		1/20 (5%)
EFC5794	SMOKERS	21/262 (8%)		14/268 (5%)
EFC4796	SMOKERS	371/3023 (12%)	170/2016 (8%)	
EFC4964	SMOKERS	17/261 (7%)	17/262 (6%)	12/261 (5%)
EFC4474	SMOKERS	24/267 (9%)	13/256 (5%)	18/260 (7%)

Table 25 and Figure 17 display the neurological adverse events during the 2nd randomization treatment period. The combined RR [95% CL] was 1.6 [1.03, 2.5] for 20mg/20mg vs. placebo/placebo for EFC4743 and 20mg/20mg vs. 5mg/plb. The p value was 0.038. The homogeneity was not significant (p=0.17).

Table 25 Percentage of patients with at least 1 neurological AE – 2nd randomization

STUDY	20mg/20mg	20mg/5mg	20mg/plb	5mg/5mg	5mg/plb	plb/plb	Fixed %W
EFC4743	21/333(6.3%)	-	17/326(5.2%)	17/300(5.7%)	19/300(6.3%)	16/298(5.4%)	58
EFC4796	28/340(8.2%)	20/335(6%)	21/342(6.1%)	25/322(7.8%)	12/322(3.7%)	-	42

Figure 17 Risk ratio of neurological AE for 20 mg rimonabant vs. comparator – 2nd randomization

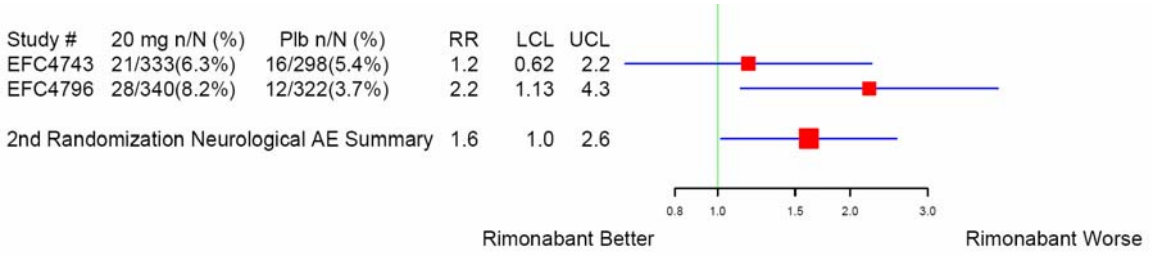


Table 26 displays the percentage of patients with at least 1 neurological AE in the phase 2 studies.

Table 26 Percentage of patients with at least 1 neurological AE – Phase 2 studies

STUDY	Rimonabant 40 mg	Rimonabant 20 mg	Rimonabant 10 mg	Rimonabant 5 mg	Placebo	Haloperidol 10 mg
DRI3388	-	8/69(12%)	4/68(6%)	4/67(6%)	3/73(4%)	-
ACT4389	53/183(29%)	-	-	-	24/183(13%)	-
ACT4855	-	9/131(7%)	-	-	16/127(13%)	-
DFI3024	-	-	-	-	2/25(8%)	6/26(23%)
DFI3067	-	-	-	-	5/22(23%)	7/22(32%)
DFI3077	-	9/72(13%)	-	-	5/26(19%)	6/25(24%)
DFI3138	-	-	-	-	3/25(12%)	7/25(28%)
PDY3796	4/23(17%)	-	-	-	8/22(36%)	-

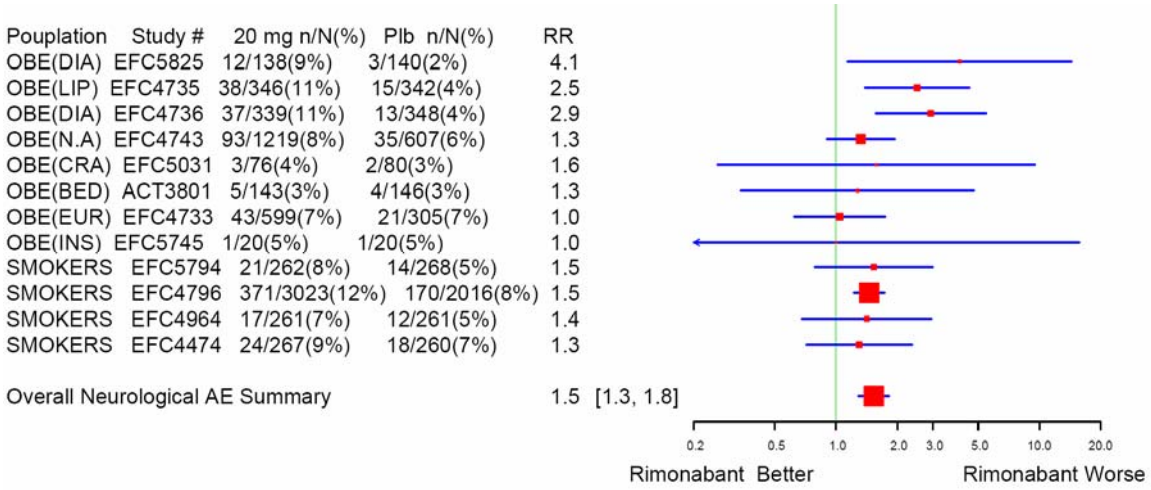
Table 27 and Figure 18 display the meta-analysis results for neurological AEs in the phase 3 studies. The incidences of neurological AEs were higher in 20 mg rimonabant-treated patients than placebo-treated patients with all RRs ≥1. The overall RR and 95% confidence interval were 1.5 [1.3, 1.8]. The relative risks of the 2 obese diabetes studies were the highest. The smoking cessation study EFC4796 with over 5,000 patients contributed the most to the overall estimate with weights of 57% in the fixed model and 37% in the random model.

Table 27 RR for incidence of neurological AE: 20 mg rimonabant vs. placebo – 12 studies

Population	Study	20 mg rimonabant	Placebo	RR	LCL	UCL	%W (fixed)	%W (random)
OBE(DIA)	EFC5825	12/138(9%)	3/140(2%)	4.06	1.17	14.07	0.8	1.9
OBE(DIA)	EFC4736	37/339(11%)	13/348(4%)	2.92	1.58	5.40	3.6	6.9
OBE(LIP)	EFC4735	38/346(11%)	15/342(4%)	2.50	1.40	4.47	4.2	7.7
OBE(CRA)	EFC5031	3/76(4%)	2/80(3%)	1.58	0.27	9.19	0.5	0.9
OBE(N.A)	EFC4743	93/1219(8%)	35/607(6%)	1.32	0.91	1.93	13.0	15.4
OBE(BED)	ACT3801	5/143(3%)	4/146(3%)	1.28	0.35	4.66	1.1	1.7
OBE(EUR)	EFC4733	43/599(7%)	21/305(7%)	1.04	0.63	1.72	7.7	9.7
OBE(INS)	EFC5745	1/20(5%)	1/20(5%)	1.00	0.07	14.90	0.3	0.4
SMOKERS	EFC5794	21/262(8%)	14/268(5%)	1.53	0.80	2.95	3.8	6.2
SMOKERS	EFC4796	371/3023(12%)	170/2016(8%)	1.46	1.22	1.73	56.6	36.5
SMOKERS	EFC4964	17/261(7%)	12/261(5%)	1.42	0.69	2.91	3.3	5.2
SMOKERS	EFC4474	24/267(9%)	18/260(7%)	1.30	0.72	2.33	5.1	7.5
Fixed				1.52	1.33	1.72	p<0.0001	
Random				1.53	1.29	1.82	p<0.0001	
homogeneity							p=0.29	

The p-value for homogeneity was 0.29. The RR was 1.52 for the fixed effects model and 1.53 for the random effects model. Both p values were less than 0.0001.

Figure 18 RR for incidence of neurological AE: 20 mg rimonabant vs. placebo

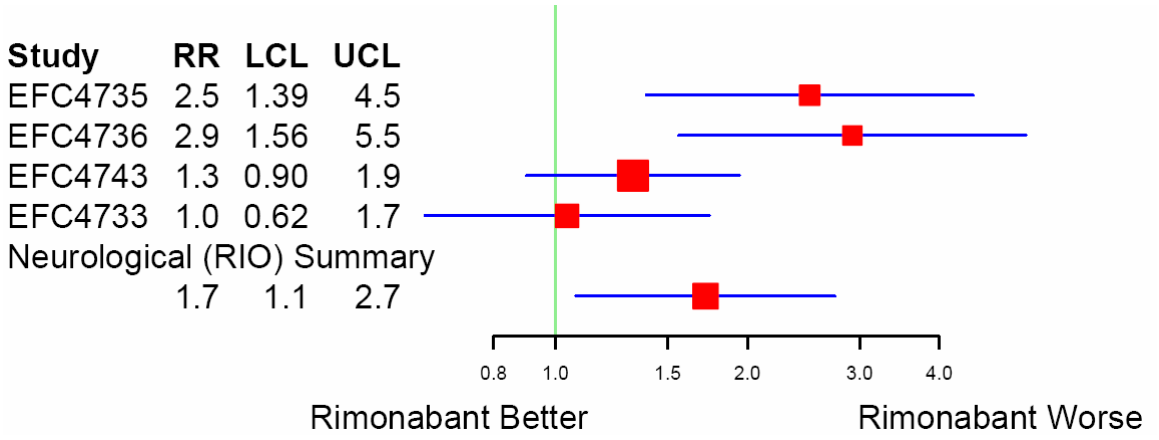


For the 4 RIO studies the p value from the random effects model was 0.02 and from the fixed effect model was <0.0001. The homogeneity test was significant (p=0.02) (Table 28 and Fig. 19).

Table 28 RR for incidence of neurological AE: 20 mg rimonabant vs. placebo – RIO studies

Population	Study	20 mg rimonabant	Placebo	RR	LCL	UCL	%W (fixed)	%W (random)
OBE(DIA)	EFC4736	37/339(11%)	13/348(4%)	2.92	1.58	5.4	13	22
OBE(LIP)	EFC4735	38/346(11%)	15/342(4%)	2.5	1.4	4.47	15	23
OBE(N.A)	EFC4743	93/1219(8%)	35/607(6%)	1.32	0.91	1.93	46	29
OBE(EUR)	EFC4733	43/599(7%)	21/305(7%)	1.04	0.63	1.72	27	25
Fixed				1.62	1.27	2.06	p<0.0001	
Random				1.72	1.09	2.72	p=0.021	
homogeneity							p=0.021	

Figure 19 RR for incidence of neurological AE: 20 mg rimonabant vs. placebo



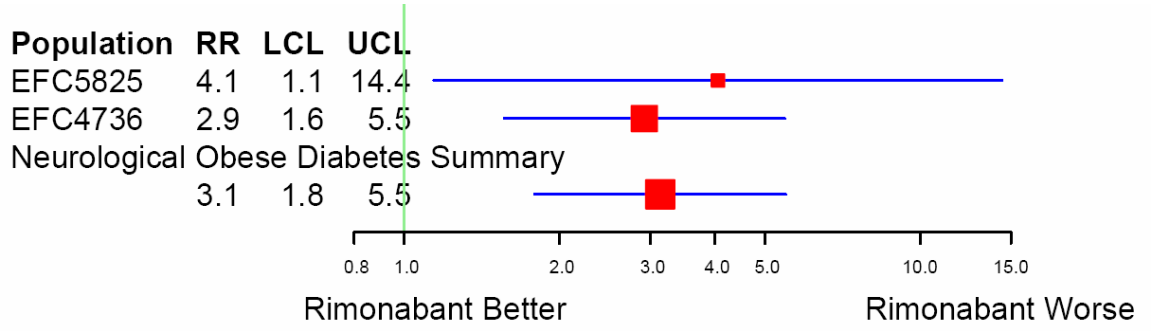
The highest neurological AE RR is in the 2 obese diabetes studies. The homogeneity test was not significant (p=0.64). The RR [95% CL] was 3.12 [1.80, 5.40]. The p value was <0.0001. Study EFC4736 was weighted approximately 80% for both fixed effects and random effects models (Table 29 & Fig 20).

Table 29 RR for incidence of neurological AE: 20 mg rimonabant vs. placebo – RIO studies

Population	Study	20 mg rimonabant	Placebo	RR	LCL	UCL	%W (fixed)	%W (random)
OBE(DIA)	EFC5825	12/138(9%)	3/140(2%)	4.06	1.17	14.07	19	20
OBE(DIA)	EFC4736	37/339(11%)	13/348(4%)	2.92	1.58	5.4	81	80

Population	Study	20 mg rimonabant	Placebo	RR	LCL	UCL	%W (fixed)	%W (random)
Fixed				3.14	1.81	5.43	p<0.0001	
Random				3.12	1.80	5.40	p<0.0001	
homogeneity							p=0.642	

Figure 20 RR for incidence of neurological AE: 20 mg rimonabant vs. placebo



2.6 Seizure

Eighteen completed trials contributed patient years in the pooled analysis and 15 studies contributed to the stratified incidence rate analysis. The 3 studies excluded from the incidence rate analysis were: an obesity PK study, a PD study (PDY3796), and 2 smoking cessation studies (ACT4389 and EFC4798). Seizures that occurred during a placebo run-in phase were excluded. Table 30 displays the studies and patient-year rates (per 100) for the 3 treatment groups.

Stratified exact tests for OR (incidence) and RR (person year) comparing 20 mg rimonabant to placebo were estimated. Studies with no events were excluded in the analysis. The risk difference (incidence) meta-analysis included those studies with no events.

For stratified analysis on OR and RR, 4 of the obesity studies contributed to the analysis which had at least 1 seizure event in one of the treatment group. The 4 seizure events in EFC4743 occurred all in the first randomized treatment. Only one controlled smoking cessation study had seizure events. One seizure in the 20 mg rimonabant group occurred during the first randomization and one placebo seizure occurred during the second randomization. The relatively rare occurrence of seizure in the smoking cessation studies prevented any meaningful estimates for that population.

The incidence rate analysis (Table 32) and person-year analysis (Table 31) showed a consistent increase of seizure risk comparing 20 mg rimonabant to placebo. In obese patients, the incidence OR [95% CL] is 4.8 [0.72, 110.8] (exact test). There were no seizure events in the placebo group of the obese diabetes studies. The OR and upper confidence limit were infinite. The risk difference [CL] is 0.19% [-0.12%, 0.5%] for obese patients (Table 36) and is 0.63% [-0.28, 1.54] for obese diabetic subjects (Table 38).

Table 30 Patient year rates by study and treatment group – completed studies

Study	Population	20 mg rimonabant	5 mg rimonabant	Placebo
ACT4855	alcohol dependence	0/26.2	-	1/23.5 (4.26%)
METATRIAL	Schizophrenia	0/4	-	2/5.7 (35.09%)
Other total		0/30.2		3/29.2
PDY3796	Obesity	-	-	0/1.6
DRI3388	Obesity	0/18.6	0/17.1	0/16.5
EFC4733	Obesity	1/761.8 (0.13%)	1/794.5 (0.13%)	0/377.8
EFC4743	Obesity	3/1154.3 (0.26%)	1/1081.2 (0.09%)	1/1172.5 (0.09%)
EFC4735	Obesity	0/266.8	0/262.3	0/268.2

Study	Population	20 mg rimonabant	5 mg rimonabant	Placebo
EFC4736	Obesity	2/269.4 (0.74%)	0/283.6	0/277.7
ACT3801	Obesity	0/57.9	-	0/59.9
EFC5031	Obesity	0/16.5	-	0/18.1
EFC5745	Obesity	0/3.1	-	0/3.1
EFC5825 (SERENADE)	Obesity	1/59.6 (1.68%)	-	0/63.9
Obesity Total		7/2608	2/2438.7	1/2259.3
ACT4389	Smokers	-	-	0/28.6
EFC4964 STRATUS-US	Smokers	0/43	0/42.3	0/42.9
EFC4474 STRATUS-EU	Smokers	0/41.5	0/39.6	0/41.1
EFC5794 STRATUS-META	Smokers	0/42	-	0/43.8
EFC4796 STRATUS-WW	Smokers	1/653.5 (0.15%)	0/684.2	1/366.3 (0.27%)
EFC4798 CIRRUS	Smokers	1/109.1 (0.92%)	-	-
Smokers Total		2/889.1	0/766.1	1/522.7
Grand Total		9/3527.3	2/3204.8	5/2811.2

Table 31: RR of Seizure in Completed Rimonabant Studies – Person Year

Indication	Rimonabant 20 mg	Rimonabant 5 mg	Placebo	20 mg vs. placebo RR [95% CL] 2-sided p value Stratified
Obesity	7/2608 (0.268%)	2/2438.7 (0.082%)	1/2259.3 (0.044%)	6.70 (1.02, 131.4) p=0.069 (4 studies)
Smoking cessation	2/889.1	0/766.1	1/522.7	0.56 (0.01, 21.86) p=1.0

Indication	**Rimonabant 20 mg**	**Rimonabant 5 mg**	**Placebo**	**20 mg vs. placebo RR [95% CL] 2-sided p value Stratified**
	(0.225%)		(0.191%)	(1 study)
ACT4855 (alcohol dependence)	0/26.2	-	1/23.5 (4.255%)	0 (0, 17.04) p=0.47
METATRIAL (Schizophrenia)	0/4	-	2/5.7 (35.088%)	0 (0, 4.95) p=0.52
All studies	9/3527.3 (0.255%)	2/3204.8 (0.062%)	5/2811.2 (0.178%)	1.69 (0.56, 5.63) p=0.42 (8 studies)

Table 32 displays seizure incidence rates in 15 of the studies with a control group. Seven of the 15 studies having at least 1 case contributed to the exact OR estimate of 20 mg rimonabant vs. placebo.

Table 32: Seizure incidence rates analysis: 20 mg rimonabant vs. placebo –Completed Studies

Population	STUDY	Rimonabant 20 mg	Rimonabant 5 mg	Placebo
Alcoholics				
	ACT4855	0/131	-	1/127 (0.79%)
Schizophrenia				
	METATRI	0/72	-	2/98 (2.04%)
Obese				
	EFC5825	1/138 (0.72%)	-	0/140
	EFC4736	2/339 (0.59%)	0/358	0/348
	EFC4733	1/599 (0.17%)	1/603 (0.17%)	0/305
	EFC4743	3/1219 (0.25%)	1/1214 (0.08%)	1/607 (0.16%)
	EFC4735	0/346	0/345	0/342
	DRI3388	0/69	0/67	0/73
	ACT3801	0/143	-	0/146
	EFC5031	0/76	-	0/80
	EFC5745	0/20	-	0/20
Smokers				
	EFC4964	0/261	0/262	0/261
	EFC4474	0/267	0/256	0/260
	EFC5794	0/262	-	0/268
	EFC4796	1/3023 (0.03%)	1/2016 (0.05%)	-
				Homogeneity test
Stratified	all studies (7)			p=0.40
OR exact	20 mg vs. placebo	1.23 [0.39, 4.22]	p=0.78	
Trend test	0, 5 mg, 20 mg		p=0.77	
				Homogeneity test
Stratified	obesity studies (4)			p=0.63
OR exact		4.80 [0.72, 110.8]	p=0.15	
Trend test	0, 5 mg, 20 mg		p=0.06	
				Homogeneity test
Stratified	diabetic studies (2)			p=1
OR exact		+∞ [0.60, +∞]	p=0.12	
Trend test	0, 5 mg, 20 mg		p=0.05	

Table 33 displays the exact test results for seizure incidence rates in the obesity studies. Only 4 studies had at least one case of seizure in either the 20 mg group or placebo group.

Table 33: Seizure OR of 20 mg rimonabant vs. placebo – 4 Obesity Studies

Study	20 mg rimonabant	5 mg rimonabant	Placebo	20 mg vs. placebo OR (95% CL) p value (Exact test)
EFC5825	1/139 (0.72%)	-	0/140	+inf [0.026, +inf]
EFC4736	2/339 (0.59%)	0/358	0/348	+inf [0.19, +inf]
EFC4733	1/599 (0.17%)	1/603 (0.17%)	0/305	+inf [0.013, +inf]

Study	20 mg rimonabant	5 mg rimonabant	Placebo	20 mg vs. placebo OR (95% CL) p value (Exact test)
EFC4743	3/1219 (0.25%)	1/1214 (0.08%)	1/607 (0.16%)	1.50 [0.12, 78.6]
Stratified OR (Exact)	20 mg vs. Placebo			4.8 [0.72, 110.6] p=0.15

Risk difference analysis included studies with 0 seizure events.

For the overall RD, study EFC4796 (in smokers) weighed 42% for the fixed effects model. The estimates were conservative by using the 5 mg rimonabant as a comparator and assigning an event to the 5 mg rimonabant which occurred during the second randomization. The RD [95% CL] was 0.02% [-0.14%, 0.19%] (Table 34, Fig 21). Limiting to the first randomization events (1 vs. 0), the RD [95% CL] was 0.04% [-0.12%, 0.21%] (Table 35, Fig 22). The estimates from outcome of relatively rare events are sensitive to any changes in event counts. For the obesity study EFC4743, all seizure events were in the first randomized treatment period.

Table 34 Seizure RD of 20 mg rimonabant vs. placebo – 14 studies

Study	20 mg Rimonabant	Placebo	RD (%)	95% LCL	UCL	Fixed % Wt
EFC5825	1/138 (0.72%)	0/140	0.72%	[-1.25%	2.70%]	2.42
EFC4736	2/339 (0.59%)	0/348	0.59%	[-0.40%	1.58%]	5.97
EFC4733	1/599 (0.17%)	0/305	0.17%	[-0.44%	0.77%]	7.02
EFC4743	3/1219 (0.25%)	1/607 (0.16%)	0.08%	[-0.34%	0.51%]	14.08
EFC4735	0/346	0/342	0%	[-0.57%	0.57%]	5.98
DRI3388	0/69	0/73	0%	[-2.72%	2.72%]	1.23
ACT3801	0/143	0/146	0%	[-1.34%	1.34%]	2.51
EFC5031	0/76	0/80	0%	[-2.48%	2.48%]	1.35
EFC4796	1/3023 (0.03%)	1/2016 (0.05%)	-0.02%	[-0.13%	0.10%]	42.03
EFC4964	0/261	0/261	0%	[-0.75%	0.75%]	4.54
EFC4474	0/267	0/260	0%	[-0.74%	0.74%]	4.58
EFC5794	0/262	0/268	0%	[-0.74%	0.74%]	4.6
ACT4855	0/131	1/127 (0.79%)	-0.79%	[-2.93%	1.35%]	2.24
METATRI	0/72	2/98 (2.04%)	-2.04%	[-5.66%	1.58%]	1.44
Fixed			0.02%	[-0.14%,	0.19%]	p=0.79

Homogeneity: p=0.99

Table 35 Seizure RD of 20 mg rimonabant vs. placebo – 14 studies 1st randomization

Study	20 mg rimonabant	Placebo	RD (%)	LCL	UCL	Fixed % Wt
EFC5825	1/138(0.72%)	0/140(0%)	0.72%	[-1.25%	2.70%]	2.42
EFC4736	2/339(0.59%)	0/348(0%)	0.59%	[-0.40%	1.58%]	5.97
EFC4733	1/599(0.17%)	0/305(0%)	0.17%	[-0.44%	0.77%]	7.02
EFC4743	3/1219(0.25%)	1/607(0.16%)	0.08%	[-0.34%	0.51%]	14.08
EFC4735	0/346(0%)	0/342(0%)	0.00%	[-0.57%	0.57%]	5.98
DRI3388	0/69(0%)	0/73(0%)	0.00%	[-2.72%	2.72%]	1.23
ACT3801	0/143(0%)	0/146(0%)	0.00%	[-1.34%	1.34%]	2.51
EFC5031	0/76(0%)	0/80(0%)	0.00%	[-2.48%	2.48%]	1.35
EFC4796	1/3023(0.03%)	0/2016(0%)	0.03%	[-0.07%	0.14%]	42.03
EFC4964	0/261(0%)	0/261(0%)	0.00%	[-0.75%	0.75%]	4.54
EFC4474	0/267(0%)	0/260(0%)	0.00%	[-0.74%	0.74%]	4.58
EFC5794	0/262(0%)	0/268(0%)	0.00%	[-0.74%	0.74%]	4.6
ACT4855	0/131(0%)	1/127(0.79%)	-0.79%	[-2.93%	1.35%]	2.24
METATRI	0/72(0%)	2/98(2.04%)	-2.04%	[-5.66%	1.58%]	1.44
Fixed			0.04%	[-0.12%	0.21%]	p=0.61

Homogeneity test: p=0.99

Figure 21 Combined RD of 20 rimonabant vs. placebo for seizure -14 studies

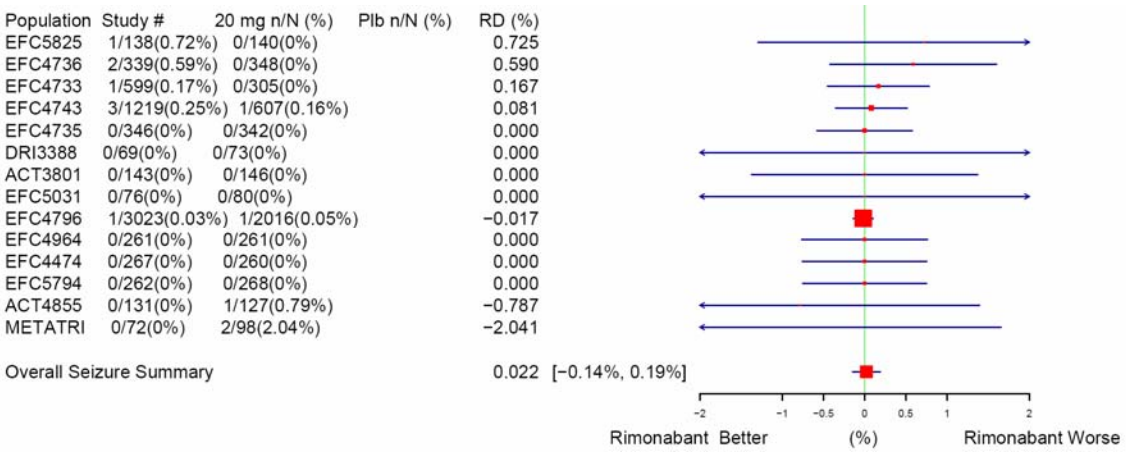


Figure 22 Combined RD of 20 rimonabant vs. placebo for seizure – 14 studies 1st randomization

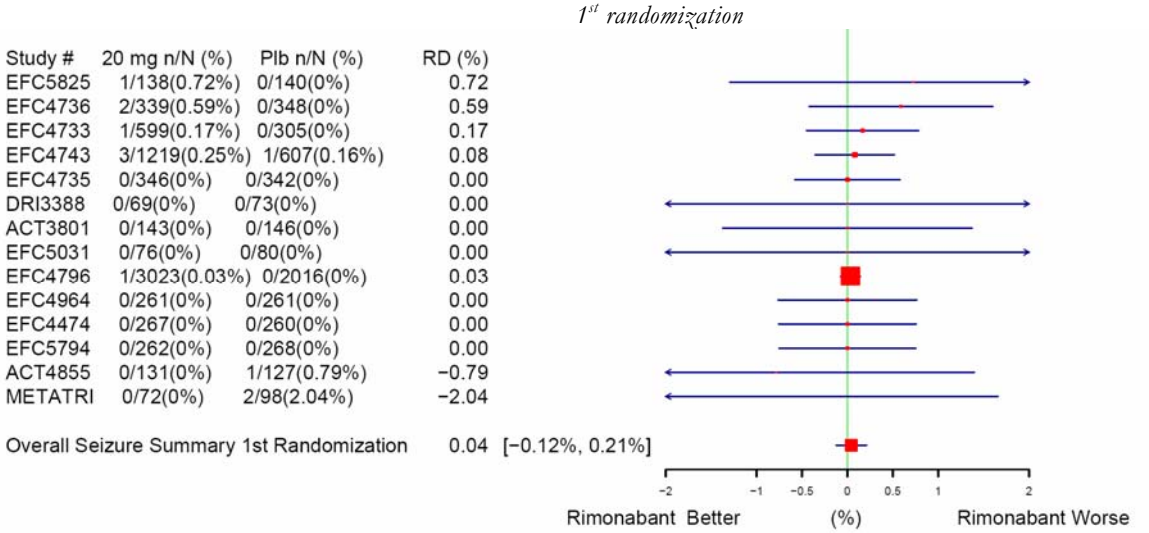


Table 36 and Figure 23 display the meta-analysis of RD in 8 obesity studies followed by the forest plots (Fig 24 & Fig 25) for the 4 RIO studies and the 2 obese diabetes studies. The RD was highest in the obese diabetics, 0.63% [-0.28%, 1.54%].

Table 36: Seizure RD of 20 mg rimonabant vs. placebo – 8 Obesity Studies

Study	20 mg Rimonabant	Placebo	RD	95% lower	CL upper	Fixed % W
EFC5825	1/138 (0.72%)	0/140 (0%)	0.72%	[-1.25%	2.69%]	5.95
EFC4736	2/339 (0.59%)	0/348 (0%)	0.59%	[-0.40%	1.58%]	14.71
EFC4733	1/599 (0.17%)	0/305 (0%)	0.17%	[-0.44%	0.77%]	17.31
EFC4743	3/1219 (0.25%)	1/607 (0.16%)	0.08%	[-0.34%	0.51%]	34.72
EFC4735	0/346 (0%)	0/342 (0%)	0.00%	[-0.57%	0.57%]	14.74
DRI3388	0/69 (0%)	0/73 (0%)	0.00%	[-2.72%	2.72%]	3.04
ACT3801	0/143 (0%)	0/146 (0%)	0.00%	[-1.34%	1.34%]	6.19
EFC5031	0/76 (0%)	0/80 (0%)	0.00%	[-2.48%	2.48%]	3.34
Combined Fixed effects			0.19%	[-0.12%	0.5%]	p=0.24

Homogeneity p=0.97

Figure 23 RD for seizure incidence: 20 rimonabant vs. placebo – 8obesity studies

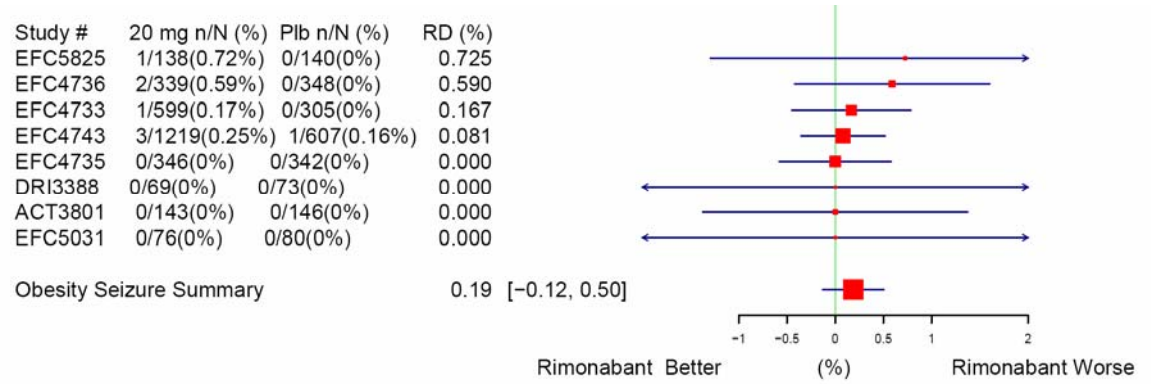


Table 37: Seizure RD of 20 mg rimonabant vs. placebo – 4 RIO Obesity Studies

Study	20 mg Rimonabant	Placebo	RD	95% lower	CL upper	Fixed % W
EFC4736	2/339 (0.59%)	0/348 (0%)	0.59%	[-0.40%	1.58%]	18.06
EFC4733	1/599 (0.17%)	0/305 (0%)	0.17%	[-0.44%	0.77%]	21.25
EFC4743	3/1219 (0.25%)	1/607 (0.16%)	0.08%	[-0.34%	0.51%]	42.61
EFC4735	0/346 (0%)	0/342 (0%)	0.00%	[-0.57%	0.57%]	18.09
Combined Fixed effects			0.18%	[-0.13%	0.48%]	p=0.25

Homogeneity p=0.75

Figure 24 RD of 20 rimonabant vs. placebo for seizure – 4 RIO obesity studies

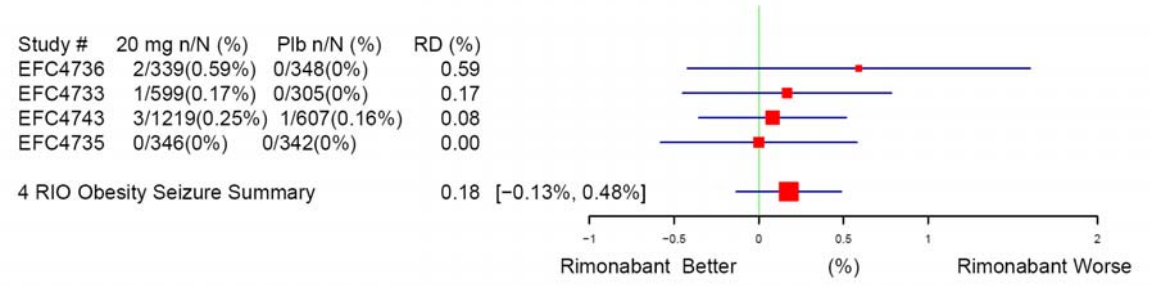


Table 38: Seizure RD of 20 mg rimonabant vs. placebo – 2 Obese Diabetes Studies

Study	20 mg Rimonabant	Placebo	RD	95% lower	CL upper	Fixed % W
EFC5825	1/138 (0.72%)	0/140 (0%)	0.72%	[-1.25%	2.69%]	
EFC4736	2/339 (0.59%)	0/348 (0%)	0.59%	[-0.40%	1.58%]	
Combined: Fixed effects			0.63%	[-0.28%	1.54%]	p=0.18

Homogeneity p=0.90

Figure 25 RD of 20 rimonabant vs. placebo for seizure – 2 obese diabetes studies