Clinical Safety

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Metabolism, Diabetes, Thrombosis
Clinical Development

Overall Clinical Safety

- **Overall Clinical Development Program**
- Overall Safety Profile & Serious Adverse Events
- Adverse Events of Interest
- Safety Conclusion

Overall Clinical Development Program Completed Studies

- A total of 15,034 patients were exposed to at least one dose of rimonabant (5 or 20 mg QD):
  - 40 Phase 1 studies (1190 subjects)
  - 6 Phase 2 studies (1008 patients)
  - 13 Phase 3 studies (12,836 patients)
    - 7447 with 20 mg exposure (1 day to 2 years)
  - In total, 6665 pt-years exposure (3478 pt-years to 20 mg)

Safety Analysis: Completed Phase 3 Studies

- Analysis followed ICH* guidelines for safety data pooling, using version 9.0 of the MedDRA dictionary:
  - Obesity pool of 7 studies (RIO-NA, RIO-EU, RIO-LIPIDS, RIO-DIABETES, EFC5031, EFC5745, ACT3801)
  - Type 2 Diabetes pool of 2 studies (RIO-DIABETES [also in Obesity pool] and SERENADE)
  - Smoking Cessation pool of 5 studies (4 STRATUS, CIRRUS)
  - Combined pool of obesity & smoking cessation programs for 12 studies (4 RIOs, EFC5031, EFC5745, ACT3801, 4 STRATUS, CIRRUS)
- Discussion today on obesity and type 2 diabetes and other populations when appropriate

* Conference on Harmonization (ICH) M4E 'Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use'

Number of Patients Exposed in Completed Phase 3 Studies (1)

Studies	Placebo	Rimonabant	
		5 mg	20 mg
Obesity			
RIO-Europe	305	603	599
RIO-North America	1233	1214	1219
RIO lipids	342	345	346
RIO-diabetes	348	358	339
ACT3801 (Binge eater)	146	-	143
REBA	80	-	76
EFC5745	20	-	20
TOTAL obesity	**2474**	**2520**	**2742**
Type 2 diabetes			
SERENADE	140	-	138
*RIO-Diabetes**	*348*	*358*	*339*
TOTAL diabetes	**488**	**358**	**477**

Number of Patients Exposed in Completed Phase 3 Studies (2)

Studies	Placebo	Rimonabant	
		5 mg	20 mg
Smoking cessation			
STRATUS-US	261	262	261
STRATUS-EU	260	256	267
STRATUS-META	268		262
STRATUS-WW	664	2351	3023
CIRRUS	-		754
TOTAL Smoking	**1453**	**2869**	**4567**
TOTAL obesity + smoking cessation + type 2 diabetes	**4067**	**5389**	**7447**

Ongoing Clinical Studies

- 11 ongoing clinical studies* as of March 1, 2007
- Blinded treatment 1:1 randomization rimonabant to placebo
- 14,280 patients exposed in clinical trials* (overall 7855 patient-years, of which 3927 patient-years are in rimonabant 20 mg group)

* Phase 1 (PDY5352, PDY6632, POP10059) and Phase 3 (EFC5107, EFC5827, EFC5828, EF5826, EFC6001, EFC5593, EFC5823, PMC_0172)

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Obesity Program: General Safety Profile (AEs in ≥ 2%* of Rimonabant-treated Patients)

%	Placebo N=2474	Rimonabant 20 mg N=2742
Any Event	**81.4**	**86.3**
Gastrointestinal disorders		
Nausea	4.7	13.6
Diarrhea	5.8	7.7
Vomiting	2.3	4.7
Nervous system disorders		
Dizziness	4.1	7.3
Psychiatric disorders		
Anxiety	2.1	5.9
Insomnia	3.4	5.8
Mood alterations with depressive symptoms	2.8	4.7
Depressive disorders	1.7	3.9
Others		
Influenza	9.1	10.3
Asthenia / fatigue	4.4	6.1
Gastroenteritis	3.5	4.5
Contusion	1.1	3.1
Hot flush	0.8	2.0

* And ≥ 1% over placebo, Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

Type 2 Diabetes Program: General Safety Profile (AEs in ≥ 2%* of Rimonabant-treated Patients)

%	Placebo N=488	Rimonabant 20 mg N=477
Any event	**73.2**	**80.7**
Gastrointestinal disorders		
Nausea	5.5	11.3
Diarrhea	5.9	7.1
Vomiting	1.8	5.5
Nervous system disorders		
Dizziness	4.3	9.6
Paresthesia	0.8	2.9
Psychiatric disorders		
Anxiety	2.9	5.2
Insomnia	2.0	4.6
Mood alterations with depressive symptoms	2.7	6.1
Depressive disorders	1.4	2.5
Others		
Asthenia / fatigue	3.9	7.1
Arthralgia	4.5	5.7
Hypoglycemia	1.4	4.0
Muscle spasms	0.6	2.7

* Note: and ≥ 1% over placebo

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Summary: General Safety Profile of Rimonabant

- In the obesity program, AEs reported in ≥ 2 % of patients were:
  - gastro-intestinal disorders (nausea/vomiting)
  - neurological disorders (dizziness)
  - psychiatric disorders (anxiety, insomnia, mood alterations, depressive disorders)
  - general disorders (asthenia/fatigue)
- In type 2 diabetes program, additional AEs included hypoglycemia, paresthesias and muscle spasms

Obesity Program: Fatal Cases (Completed Studies)

Cause of Death	Placebo N=2474	Rimonabant 5 mg N=2520	Rimonabant 20 mg N=2742
Deaths n (%)	**3 (0.12)**	**3 (0.12)**	**4 (0.15)**
Cardiac arrest	-	1	-
Cardiac failure	-	-	1
Coronary artery disease	-	-	1
Road traffic accident	-	-	1
Completed suicide	-	1	-
Uterine cancer	-	-	1
Septic shock	-	1	-
Pulmonary embolism	1	-	-
Cerebral hematoma /CVA	1	-	-
Cerebral hemorrhage	1	-	-

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

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Adverse Events of Interest

- Psychiatric disorders
  - depression-related events
  - suicidality-related events
  - anxiety disorders
- Neurological adverse events
  - overall
  - multiple sclerosis
  - seizures

Depressive-Related Events in Obesity Phase 3 Studies – Specific Methodology

- Prospective monitoring in RIO studies
  - to facilitate psychiatric consultation in a non psychiatric environment
  - to increase the sensitivity of detection of depressive events through regular patient self assessment scale (HAD)
- Retrospective assessment through a specific questionnaire
  - focus on outcome and associated symptoms including suicide attempt/ideation

Obesity Program: Depressive-Related Events

%	Placebo N=2474	Rimonabant 20 mg N=2742
Depressed mood disorders and disturbances	**4.5**	**8.4**
Mood alterations with depressive symptoms	2.8	4.7
Depressive disorders	**1.7**	**3.9**

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

Obesity Program: Main Characteristics of Depressed Mood Disorders and Disturbances

	Mood Alterations with Depressive Symptoms		Depressive Disorders	
	Placebo N=70	Rimonabant 20 mg N=129	Placebo N=43	Rimonabant 20 mg N=106
Past history of depressive disorders	16%	14%	40%	42%
Treatment discontinuation	26%	26%	58%	61%
Corrective therapy (CT)	35%	29%	72%	72%
Time to recovery + CT (median)	119	91	73	131
Time to recovery – CT (median)	42	50	103	30
Hospitalization (n)	0	0	1	4

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

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Impact of Past History of Depressive Disorders

N (%)	No Past History of Depressive Disorders		Past History	
	Placebo N=2282	Rimonabant 20 mg N=2507	Placebo N=192	Rimonabant 20 mg N=235
Any Psychiatric Event	**248 (10.9)**	**584 (23.3)**	**55 (28.6)**	**108 (46.0%)**
Mood alterations with depressive symptoms	59 (2.6)	110 (4.4)	11 (5.7)	19 (8.1)
Depressive disorders	**26 (1.1)**	**61 (2.4)**	**17 (8.9)**	**45 (19.1)**
Anxiety	44 (1.9)	132 (5.3)	7 (3.6)	29 (12.3)
Insomnia	70 (3.1)	139 (5.5)	13 (6.8)	20 (8.5)

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

Depression-Related Events: Summary

- Two different types of events:
  - mood alterations
    - less need for corrective treatment
  - depressive disorders
    - more frequent corrective treatment
    - hospitalizations (1 placebo, 4 rimonabant)
- Depressive disorders more frequently reported with rimonabant 20 mg compared to placebo (3.9% vs 1.7%)
- Main predictor was a past history of depression; (2.4% vs. 1.1%) if no past history

Suicidality-Related Events Methods of Analysis

- In agreement with FDA, the sponsor followed C-CASA: Columbia-Classification of Adult Suicidality Assessment validated algorithm* to search for suicide-related events in completed double-blind, randomized studies
- Blinded narratives of adverse events from 22 studies sent for assessment by C-CASA:
  - removed information on patients, study name, study drug, dates and chronology
  - Phase 2 (9 studies) & completed Phase 3 (13 studies) studies

* FDA Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee, September 13, 2004

Categorization of "Suicidality" C-CASA

Independent and blind categorization by experts as follows:

1: Completed suicide

2: Suicide attempt

3: Preparatory acts toward imminent suicide behavior

4: Suicidal ideation

5: Self-injurious behavior, intent unknown

6: Not enough information (fatal)

7: Self-injurious behavior, no suicidal intent

8: Other: accident, psychiatric, medical

9: Not enough information (non fatal)

Suicidality Assessment per C-CASA in All Indications

All completed Phase 2 and 3 Studies* as of March 2007

N (%)	Placebo (N=3411)	Rimonabant 5 mg (N=5254)	Rimonabant 20 mg (N=7851)
Definitely suicidal behavior/ideation			
(Categories 1 to 4)	21 (0.62)	11 (0.21)	48 (0.61)
Possibly suicidal			
(Categories 5, 6, 9)	2 (0.06)	1 (0.02)	5 (0.06)

- Total = 88 cases under placebo or rimonabant

* Phase 2 studies: obese, smoking, alcohol, schizophrenia, and Phase 3 studies: RIO, REBA, SERENADE, EFC5745, ACT3801 and Smoking

Suicidality Assessment per C-CASA in Obesity and Diabetes

All completed Phase 2 and 3 Studies* as of March 2007

Category ** N (%)	Placebo (N=2214)	Rimonabant 5 mg (N=2720)	Rimonabant 20 mg (N=3081)
Definitely suicidal behavior/ideation	***8 (0.36)***	***8 (0.29)***	***20 (0.65)***
2 Suicide attempt	0 (0)	0 (0)	1 (0.01)
4 Suicidal ideation	8 (0.36)	8 (0.29)	19 (0.62)
Possibly suicidal	***1 (0.05)***	***1 (0.04)***	***2 (0.06)***
6 Not enough information (fatal)	0 (0)	1 (0.04)	0 (0)
9 Not enough information (non fatal)	1 (0.05)	0 (0)	2 (0.06)

* DRI3388, PDY3796, DRI5747, EFC4733, EFC4735,EFC4736, EFC4743, ACT3801, EFC5031, EFC5745, EFC5825, ACT4389, EFC4474, EFC4964, EFC4796, EFC5794, DRI3388, ACT4855, EFC4798, Ph1 studies as a single strata, Run-in periods in RIO studies

**Category including at least one event

Odds Ratio for Suicidality (95%)

Method	FDA	Sponsor
Overall	**1.9 (1.1, 3.1)**	**1.3 (0.8, 2.3)**
Smoker	3.9 (1.2, 16.8)	1.0 (0.2, 4.9)
Other*	1.4 (0.4, 4.4) 0.97 (0.2, 5.7)	1.1 (0.4, 2.8)
Obesity and diabetes	1.8 (0.8, 3.8)	1.6 (0.7, 3.5)

*for schizophrenia and alcohol study

Investigator-Reported Suicides

	Completed Trials
Investigator Reported Suicides	1 (5 mg)
Patient-Years	6979
Events/100K Patient Years (95% CI)	14 [0.0, 80]

As of May 2007: two reported cases of suicide in ongoing clinical trials and one post-market case of suicide reported (28 May 2007) via second-hand information in a patient allegedly receiving rimonabant.

BMI > 30 = 13 per 100,000 pt-years: Mukamal, et al. Body Mass Index and Risk of Suicide Among Men. *Arch Intern Med* 2007; 167:468-475.

Completed Suicide in Ongoing Studies

Study Sex Gender TT group	Exposure on rimonabant	Past History	Clinical Description	Stressors
STRADIVARIUS Male 36 yrs 20mg *received:* *Aug 2006*	10 months	Myocardial infarction 1week prior to inclusion	About 8 months after starting study drug, patient with no psychiatric history presented a non-serious mild depressive mood., irritability and fatigue. Serious professional and financial stressors. Depression worsened within 3months.No corrective treatment. No psychiatrist or specialist consulted	Financial problems, overworked
CRESCENDO Male 77 yrs 20mg *received:* *22 May 2007*	45 weeks	Depression at age of 40. additional further episodes	About 10 months after study start, the patient became depressed. He discontinued rimonabant on his own. He visited a psychiatrist who prescribed SSRI and committed suicide 1 week later. Psychiatrist evaluation revealed depression and loss of energy/interest and no associated suicidal ideation.	Marital difficulties Physical handicap due to worsening of neuropathy

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Completed Suicide in Completed Study

Study Sex Gender TT group	Suicidal Behavior (Date of Onset)	Past History	Description	Stressors
RIO NA Male 63 yrs 5mg *received:* *March 2002*	Gunshot wound (D157) "Apparent suicide" according to investigator	Depressive symptoms Anxiety	"At last visit: no sign of despondency, hopelessness, or outwards sign the patient was suicidal" From nurse: can't eat, slept 30 hours Was found dead, in front of his house."	Past involvement in a federal witness protection program, Pending court decision

Patients with Suicidal Behavior/Ideation SAEs** Assessed per C-CASA in Ongoing Phase 3b Studies*

Category N (%)	Placebo (N~7980)	Rimonabant 20 mg (N~7980)
Definitely suicidal behavior/ideation	***11 (0.14)***	***24 (0.30)***
1 Completed suicide	0 (0.0)	2 (0.03)
2 Suicide attempt	2 (0.03)	0 (0.0)
4 Suicidal ideation	9 (0.11)	22 (0.28)

- Total = 35 cases under placebo or rimonabant

* Phase 3 studies: EFC5107, EFC5827, EFC5828, EF5826, EFC6001, EFC5593, EFC5823, PMC_0172 and EFC5749

** Includes relevant SAE data through 29 May 2007

Suicidality Summary
Obesity and Diabetes Studies

- An imbalance was seen in obesity and diabetes studies for “definitely suicidal behavior/ideation”.
  - (0.65%) vs. (0.36%)
- Suicidal ideation was always associated with depression or adjustment disorders
- A causal link has not been established between suicidality and the use of rimonabant

Obesity Program: Frequency of Anxiety Symptoms and Panic Disorders

%	Placebo N=2474	Rimonabant 20 mg N=2742
Anxiety symptoms	**3.8**	**9.0**
Anxiety	2.1	5.9
Stress	1.5	1.6
Nervousness	0.3	1.2
Agitation	< 0.1	0.4
Tension	0	< 0.1
Panic disorders	**< 0.1**	**0.8**
Panic attack	< 0.1	0.7
Panic disorder	0	<0.1
Panic reaction	0	<0.1

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

Obesity Program: Main Characteristics of Anxiety Disorders and Symptoms

	Placebo N=2474	Rimonabant 20 mg N=2742
Anxiety Disorders and Symptoms	N=100	N=278
Past history	9%	7.9%
Treatment discontinuations	14%	19.8%
Corrective therapy	48%	41%
Time to recovery + CT (median)	65	43
Time to recovery – CT (median)	45	35
Resulting in hospitalization (n)	0	1

Obesity program: 4 RIOs, EFC5031, EFC5745, ACT3801

Obesity Program: Most Frequent Neurological Adverse Events

%	Placebo N=2474	Rimonabant 20 mg N=2742
Any event	**12.5**	**20.2**
Sensory changes	**9.3**	**14.8**
Dizziness	4.1	7.3
Paresthesia/Hypoesthesia	1.7	2.8
Sciatica	0.6	1.2
Motor impairment	**2.3**	**3.4**
Tremor	<0.1	0.9
Cognitive difficulties	**2.1**	**4.1**
Memory loss	0.7	1.5

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

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Obesity Program: Neurological Adverse Events Leading To Discontinuation > 0.1%

	Placebo N=2474	Rimonabant 20 mg N=2742
Any Event %	**16 (0.6)**	**61 (2.2)**
Sensory changes	**8 (0.3)**	**38 (1.4)**
Dizziness / Vertigo	3 (0.1)	21 (0.8)
Paresthesia/Hypoesthesia	1 (<0.1)	12 (0.4)
Motor Impairments	**5 (0.2)**	**11 (0.6)**
Tremor	0 (0)	5 (0.2)
Cognitive Difficulties	**3 (0.1)**	**18 (0.7)**
Memory loss	2 (<0.1)	6 (0.2)

Obesity program: 4 RIO, EFC5031, EFC5745, ACT3801

Confirmed New Occurrences of Multiple Sclerosis (MS)

Reported MS	Completed Trials	Ongoing Trials*
Placebo (n)	1	0
Patient-Years	3451	3927
Events/100K Patient Years (95% CI)	29 (1, 161)	0 (0, 97)
Rimonabant 5 mg (n)	2	NA
Rimonabant 20 mg (n)	0	0
Patient-Years (5 mg and 20 mg)	6979	3927
Events/100K Patient Years (95% CI)	29 (3, 103)	0 (0, 97)

* As of March 1, 2007

** As of end-April 2007 (post-marketing): No case reports of confirmed multiple sclerosis, 1 case of bilateral papillitis [optic neuritis] 1 month after starting rimonabant reported as potential MS

Incidence rate of MS in the general population is 7.5 per 100,000 person-years (Mayr et al, 2003)

Multiple Sclerosis in Completed Studies

- Suspected MS (20 mg)
  - 49 year old woman evaluated for balance disorder; MRI scan not consistent with MS. Updated information 3.5 years after end of study reveals no new events and normal yearly evaluations.
- Pre-existing MS with relapse (20 mg)
  - 42 year old woman with MS diagnosed almost 5 years prior to entering the study. Relapse on treatment similar to relapses prior to and after study.

Seizure Evaluation

- Exclusion Criteria in Phase 3 Studies
  - patients with treated epilepsy
  - 72 patients with a seizure history were randomized in Phase 3.
- Methodology
  - adverse events from the HLGT* MedDRA (9.0) “seizures (incl subtypes)” up to 75 days post-dosing in all studies
  - string search** to for potential cases (completed & on-going trials)
  - independent, blind review by neurology experts with questions to investigators for additional information
    - classification of cases as “possible or likely”, or “unlikely”

* HLGT: High Level Group Term

** *“convuls”, “petit mal”, “grand mal”, “epilep”, “tonic clonic”,“focal”, “partial”, “generaliz”, “absence”, “conscious”, seizur, “ictus”, “ictal”, “clon”*

Seizures in Completed Studies: FDA and Sponsors Analysis

- FDA analysis
  (Table 31 of FDA BP)
  - included only studies (n=8) with a report of seizure
  - excluded cases in placebo run-in phase (2 cases) and > 3 months after study end (1 placebo case).
  - included cases in non-placebo controlled phases or studies (2 cases in 20 mg).
  - compared rimonabant 20mg versus placebo.
- Sponsor analyses
  - included all completed studies (Phase 1, 2 ,3) with/without events.
  - included all reported seizures whatever the phase.
  - compared rimonabant all doses versus placebo.
  - 2 Analyses performed:
    - all seizure cases (unlikely, likely or possible)
    - likely or possible seizures as assessed by external experts

Incidence Rate of Seizures in Completed Studies

- 19 cases were reviewed by the experts:
- 14 were assessed as likely or possible seizures
- 5 were assessed as unlikely seizures

Number of events / Extent of exposure in patient-years [a] (%)				Relative Risk (90% confidence interval) Rimonabant vs Placebo
	Rimonabant			
Placebo (3451)	5 mg (3263)	20 mg (3597)	All doses * (6979)	
Analysis of the 19 cases in the completed studies				
8 (0.23%)	2 (0.06%)	9 (0.25%)	11 (0.16%)	0.68 (0.31, 1.51)
Analysis of the 14 cases assessed as "likely/possible seizures" by the experts				
6 (0.17%)	2 (0.06%)	6 (0.17%)	8 (0.11%)	0.66 (0.27, 1.68)

(a) Patient exposure includes placebo run-in periods and non controlled study periods

Unstratified analysis including placebo run-in

* Only doses for which there is at least one event are shown.

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Incidence Rate (Patient-Years) of Seizures in Completed Studies

FDA Analysis : 8 studies, 20 mg versus Placebo
Excludes 2 placebo run-in cases and one late event.
Includes two 20 mg cases in non-placebo controlled studies.

Placebo	20mg	RR 20 mg vs. placebo (95% CI)
5/2811	9/3527	1.69 (0.56, 5.63)

Sponsor analysis: all studies, all cases (unlikely, possible, likely)
Includes all reported cases

Placebo (a)	20mg	All doses	RR 20 mg vs. placebo (90% CI)	RR All doses vs. placebo (90% CI)
8/3451	9/3597	11/6979	1.08 (0.48,2.47)	0.68 (0.31, 1.51)

(a) Patient exposure includes placebo run-in periods and non controlled study periods

Seizures – Ongoing Studies

- 8 cases of possible seizures have been reported
- All were blindly adjudicated by the same experts and then unblinded
  - possible / likely: 20 mg (4) and placebo (2)
  - unlikely: 20 mg (2)
- Estimated incidence in patient-years, in 20 mg:
  - 6/3927 (0.15%) for all reported cases
  - 4/3927 (0.10%) for 'possible/likely' cases

  Similar to that observed in completed studies (0.25%)

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- **Safety Conclusion**

Overall Safety Conclusion (1)

- Rimonabant is well-tolerated in the proposed patient populations with a defined safety profile
- **Depression**
  - reported more with rimonabant (3.9% vs. 1.7%)
  - past history of depression predicts recurrent depression for both placebo and rimonabant
- **Suicidality**
  - imbalance in suicidal ideation
  - always associated with treatable depression or adjustment disorders

Overall Safety Conclusion (2)

- **Overall Neurological Adverse Events**
  - most frequent AEs: dizziness, paresthesia/hypoesthesia, tremor, memory loss
  - no imbalance in serious neurological events
- **Seizures**
  - no increased seizure rate with rimonabant
  - treated epileptic patients excluded from Phase 3 completed studies
  - caution in patients being treated for epilepsy
  - treated epileptic patients are included in ongoing studies

Overall Safety Conclusion: Safety Perspective (3)

- Sibutramine Package Insert (weight loss)
  - *"**Psychiatric**: Cases of depression, suicidal ideation, and suicide have been reported rarely on patients treated with sibutramine. However, the relationship has not been established between the occurrence of depression and/or suicidal ideation and the use of sibutramine. If depression occurs during treatment with sibutramine, further evaluation may be necessary."*

Overall Safety Conclusion (4)

- Ongoing worldwide post-marketing experience and risk-management program has shown no new safety signals