Food and Drug Administration
Center for Drug Evaluation and Research
Hilton Silver Spring, 8727 Colesville Road, Silver Spring, Maryland.

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee meeting on June 13, 2007.

On June 13, 2007, the committee discussed the efficacy and safety of new drug application (NDA) 21–888, proposed trade name Zimulti (rimonabant), 20 milligrams tablets, Sanofi-Aventis, as an adjunct to diet and exercise for obesity management in patients with a body mass index equal to or greater than 30 kilograms (kg) per square meter, or a body mass index equal to or greater than 27 kg per square meter if accompanied by at least one cardiovascular risk factor.

These summary minutes for the June 13, 2007 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on Tuesday, June 19, 2007.

I certify that I attended the June 13, 2007 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Miller, M.P.H., R.N.
Designated Federal Official

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Clifford J. Rosen, M .D.
(Acting) Chair

_____
Date

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 13, 2007 at the Hilton Silver Spring, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and the sponsor (Sanofi-Aventis). The meeting was called to order by Clifford J. Rosen, M.D (Acting Committee Chair); the conflict of interest statement was read into the record by Cathy A. Miller, M.P.H. (Designated Federal Official). There were approximately 250 persons in attendance. There were three speakers for the Open Public Hearing session.

Issue: The committee discussed the efficacy and safety of new drug application (NDA) 21–888, proposed tradename Zimulti (rimonabant), 20 milligrams tablets, Sanofi-Aventis, as an adjunct to diet and exercise for obesity management in patients with a body mass index equal to or greater than 30 kilograms (kg) per square meter, or a body mass index equal to or greater than 27 kg per square meter if accompanied by at least one cardiovascular risk factor.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting): Kenneth D. Burman; M.D.; Thomas O. Carpenter, M.D.; Jessica W. Henderson, Ph.D.; Katherine M. Flegal, Ph.D.; Clifford J. Rosen, M.D.; Michael Proschan, Ph.D.

Special Government Employee Consultants (Voting): Wayne K. Goodman, M.D.; Philip S. Wang, M.D.; Ph.D.; Melanie Coffin (Patient Representative); Domenic A. Ciraulo, M.D.; Robert A. Kreisberg, M.D.; Paul D. Woolf, M.D.; Jules Hirsch, M.D.; Sid Gilman, M.D., F.R.C.P.

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Non-Voting):
Steven W. Ryder, M.D. (Industry Representative)

Guest Speaker (Non-Voting):
Kelly Posner, Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present: Nelson B. Watts, M.D. (Chair); Sonia Caprio, M.D.; Margaret E. Wierman, M.D.; Morris Schambelan, M.D.

FDA Participants (Non-Voting): Mary H. Parks, M.D.; Eric G. Colman, M.D.; Curtis Rosebraugh, M.D.; Amy Egan, M.D., M.P.H.; Karen Davis-Bruno, Ph.D.

Designated Federal Official:
Cathy A. Miller, M.P.H., R.N.

Open Public Hearing Speakers:
Sidney M. Wolfe, M.D., Director, Public Citizen's Health Research Group
Lynn McAfee, Director, Medical Advocacy Council on Size and Weight Discrimination
Caroline M. Apovian, M.D., Secretary/Treasurer, The Obesity Society

The agenda was as follows:

Call to Order and Introductions	**Clifford Rosen, M.D.** (Acting) Committee Chair

Conflict of Interest Statement	**LCDR Cathy A. Miller, M.P.H.** Designated Federal Official Endocrinologic and Metabolic Drugs Advisory Committee
Introduction/Background	**Eric G. Colman, M.D.** Deputy Director, FDA/CDER Division of Metabolic and Endocrine Products

PRESENTATIONS:

Guest Speaker:

Suicidality Issues in Clinical Trials: Columbia Suicidal Adverse Event Identification in FDA Safety Analyses	**Kelly Posner, Ph.D.** Department of Child Psychiatry New York State Psychiatric Institute New York, NY

Sponsor Presentations - Sanofi-Aventis:

Introduction	**Richard Gural, Ph.D.** Vice President, Global Regulatory Affairs, Sanofi-Aventis
Mechanism of Action	**Kenneth P. Mackie, M.D.** Linda and Jack Gill Chair of Neuroscience, Professor of Psychology, Department of Psychological & Brain Sciences Indiana University
Medical Need and the Clinical Efficacy of Rimonabant	**Pierre Rosenzweig, M.D.** Vice President, International Clinical Development Internal Medicine, Sanofi-Aventis
Clinical Safety of Rimonabant	**Paul Chew, M.D.** Vice President, International Clinical Development Metabolism, Diabetes, and Thrombosis, Sanofi-Aventis
Proposed Risk Management Plan	**Richard Gural, Ph.D.**
Benefit/Risk of Rimonabant	**Louis Aronne, M.D.** Clinical Professor of Medicine Weill Medical College of Cornell University
	Clarifying Questions from the Committee
	Break

FDA Presentations:

. Preclinical Evaluation of Rimonabant	**Karen Davis-Bruno, Ph.D.** Pharmacologist, FDA/CDER Division of Metabolic and Endocrine Drug Products
	Clarifying Questions from the Committee
	Lunch
	Open Public Hearing

FDA Presentations (Continued):

Clinical Efficacy and Safety	**Amy Egan, M.D., M.P.H.**

of Rimonabant	Medical Officer, FDA/CDER Division of Metabolic and Endocrine Drug Products
	Break
	Committee Discussion and Questions
	Adjourn

Questions to the Committee:

1. Please discuss your level of concern regarding rimonabant and psychiatric adverse events, in particular depression and suicidality, and neurological adverse events, in particular seizures, and the reasons behind your thinking on these issues.

The committee identified concerns discussed by the committee included:

- ***Concerns about what is not yet known with this first in class drug; concerns that the sponsor did not have the representative number of patients to meet the target 1500***
- ***Concerns were raised about the generality of defining terms such as seizures, tremors, and other neurological symptoms, in the reporting of adverse events; concerns about the quality of the safety data***
- ***Reports of the psychiatric effects are too high and too serious especially given the attrition rate in the trials, the implication being data is lost on adverse effects, depression and anxiety***
- ***Data presented showed a doubling of risk of depression in the subgroup of patients who did not even have a history of psychiatric illness; need to pursue additional subgroup analyses***
- ***With concerns identified, the suggestion was made to identify a more stringent set of prescribing guidelines for a subgroup of patients that may benefit from the drug***
- ***Need to have additional data on the fate of patient terminated from treatment because of depression {long-term fate of the treatment for depression} and the possibility of combining rimonabant treatment with an anti-depressant***
- ***Quality of life data concern, in terms of risk/benefits of treatment; the point was also raised that because some of the data was carried over from the last visit before they dropped out, we may be underestimating the impairment of quality of life***
- ***Additional concerns included the high drop-out rate, the potential long term effects of the agent including effects on reproduction and hypertension; the studies done involved mainly Caucasian which may or may not apply to other groups***
- ***There was general agreement among the committee that there needs to be more long-term data; the concern being that that of having limited 2-year study data being used to assess a drug that would be used long-term***
- ***A suggestion was made that future studies include an agreement between sponsor and the Agency on method of analysis used to avoid conflicts presented today and to have as much specificity in the guidance as possible (i.e. # of patients at one-year period; two-year period)***

(See transcript for detailed discussion)

2a. Do you believe that the currently available data sufficiently characterize rimonabant's safety profile **(vote requested)?**

YES: 0 NO: 14

2b. If no, please discuss what additional data should be obtained.

- ***Dr. Posner presented helpful information [C-CASA] that can be used to measure in a systematic way***
- ***More specific information about neurological information, for example, what the patient means when he/she says 'dizzy'; better characterization of seizures from the observer or the patient themselves***
- ***More safety data – prospective study on subgroup of patients on drug in Europe to collect more data***
- ***Need to take different approach to the adverse effects - treat like an outcome study to get the best scales together to measure anxiety, depression, and other psychiatric systems, along with the C-CASA methodology, to measure AEs.***
- ***More information needed on the patients that have been discontinued because they have been put on anti-depressants; need to continue following these patients [continue in study without active drug]***
- ***Need to work closer to design studies that would be satisfying in addressing many of the issues of concern cited such as specificity of AE definition but little can be done about mining information in this respect for trials already underway***

(See transcript for detailed discussion)

3a. Based on the currently available data, do you believe rimonabant has a favorable risk-benefit profile and should be approved for the indication of weight management in individuals with a body mass index of $\geq$ 30 kg/m^2 and $\geq$ 27 kg/m^2 when accompanied by at least one co morbid condition **(vote requested)?**

YES: 0 NO: 14

3b. If no, please explain why and discuss what additional information the sponsor could obtain that might improve rimonabant's risk-benefit profile.

- ***The Chair was satisfied that sufficient comments were provided in earlier discussion regarding the need for additional information; the committee did re-emphasize the need for more data.***

The committee adjourned at approximately 4:45 P.M.

(See transcript for detailed discussion)