Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
February 22, 2012

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed the safety and efficacy of new drug application (NDA) 22–580, proposed trade name QNEXA (phentermine/topiramate) Controlled-Release Capsules, manufactured by VIVUS, Inc., as an adjunct to diet and exercise for weight management in patients with a body mass index (BMI) equal to or greater than 30 kilograms (kg) per square meter or a BMI equal to or greater than 27 kg per square meter if accompanied by weight-related co-morbidities.

These summary minutes for the February 22, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on 4/6/2012

I certify that I attended the February 22, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/Signed/
Paul T. Tran, R.Ph
(Designated Federal Officer, EMDAC)

/Signed/
Abraham Thomas, M.D., M.P.H.
(Chair, EMDAC)

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
February 22, 2012

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on February 22, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the Food and Drug Administration (FDA) website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/default.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA Center for Drug Evaluation and Research, met on February 22, 2012 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Vivus, Inc. The meeting was called to order by Abraham Thomas, M.D., M.P.H. (Chair), and the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Officer). There were approximately 225 people in attendance. There were ten Open Public Hearing speakers.

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 22–580, proposed trade name QNEXA (phentermine/topiramate) Controlled-Release Capsules, manufactured by VIVUS, Inc., as an adjunct to diet and exercise for weight management in patients with a body mass index (BMI) equal to or greater than 30 kilograms (kg) per square meter or a BMI equal to or greater than 27 kg per square meter if accompanied by weight-related co-morbidities.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Erica Brittain, Ph.D.; David Capuzzi, M.D., Ph.D.; Eric Felner, M.D.; Edward Gregg, Ph.D.; Abraham Thomas, M.D., M.P.H. (*Chair*); Lamont Weide, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):
Vera Bittner, M.D.; Ellen Seely, M.D.; Ida Spruill, Ph.D., R.N. (*Consumer Representative*)

Acting Industry Representative to the Committee (Non-voting):
Mads F. Rasmussen, M.D., Ph.D. (*Acting Industry Representative*)

Temporary Members (Voting):
Ken Burman, M.D.; Robert Clancy, M.D.; Melanie Coffin (*Patient Representative*); Janet Cragan, M.D., Ph.D.; Katherine Flegal, Ph.D.; Allison Goldfine, M.D.; Jessica Henderson, Ph.D. (*Acting Consumer Representative*); Sanjay Kaul, M.D.; Michael Lauer, M.D.; Elaine Morrato,

Dr.PH, M.P.H., C.P.H.; Sonja Rasmussen, M.D., M.S.; Michael Rogawski, M.D., Ph.D.; Robert Smith, M.D.; Myrlene Staten, M.D.; Almut Winterstein, Ph.D.; Susan Yanovski, M.D.

Speaker (Non-Voting):
Suzanne Gilboa, Ph.D.

FDA Participants (Non-voting):
Eric Colman, M.D.; John Jenkins, M.D.; Claudia B. Karwoski, Pharm.D. Mary Roberts, M.D.; Mary H. Parks, M.D.; Joyce Weaver, Pharm.D.

Designated Federal Officer: Paul Tran, R.Ph

Open Public Hearing Speakers:
Denise Bruner, M.D., FASBP (American Society of Bariatric Physicians); Christopher Gallagher (American Society for Metabolic & Bariatric Surgery); George Grunberger, M.D., FACP, FACE (American Association of Clinical Endocrinologists); Kelly Close (Editor in Chief, diaTribe); Morgan Downey, J.D. (The Downey Obesity Report); Joe Nadglowski (President/CEO, Obesity Action Coalition); Kate Ryan, MPA (National Women's Health Network); Sidney Wolfe, M.D. (Director of Public Citizen's Health Research Group); Diana Zuckerman, Ph.D. (President, National Research Center for Women & Families/Cancer Prevention and Treatment Fund); Ted Kyle, R.Ph, M.B.A. (The Obesity Society ConscienHealth)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Abraham Thomas, M.D., M.P.H., FACP** Chair, EMDAC
Conflict of Interest Statement	**Paul T. Tran, R.Ph** Designated Federal Officer, EMDAC
Introduction/Background	**Eric C. Colman, M.D.** Deputy Director Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation (ODE) II Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATION	**Vivus, Inc.**
Introduction	**Peter Tam** President, Vivus, Inc.
Review of Efficacy	**Wesley Day, Ph.D.** Vice President, Clinical Development Vivus, Inc.
Review of Safety	**Neil Gesundheit, M.D., M.P.H.** Stanford University School of Medicine Stanford, California
Review of Cardiovascular Safety	**Peter Kowey, M.D.**

	Lankenau Medical Center Wynnewood, Pennsylvania
Review of Teratogenicity	**Gary Shaw, Ph.D.** Professor Division of Neonatal and Developmental Medicine Department of Pediatrics Stanford University School of Medicine Palo Alto, California
Clinical Perspective On Teratogenicity	**Anthony Scialli, M.D.** Tetra Tech Sciences Arlington, Virginia
Cardiovascular Perspective	**A. Michael Lincoff, M.D.** Cardiovascular Medicine, Cleveland Clinic Cleveland, Ohio
Medical Need and Risk Benefit	**Arya Sharma, M.D., Ph.D., D.Sc.** Obesity Research & Management University of Alberta Royal Alexandra Hospital Edmonton, Canada
Clarifying Questions from the Committee	

BREAK

FDA PRESENTATION

Review of Phentermine/Topiramate (PHEN/TPM) Efficacy and Cardiovascular Safety	**Mary D. Roberts, M.D.** Clinical Reviewer DMEP, ODE II, OND, CDER, FDA

SPEAKER PRESENTATION

Use of Topiramate in Pregnancy and Risk of Oral Clefts	**Suzanne M. Gilboa, Ph.D.** National Center on Birth Defects and Developmental Disabilities (CDC) Atlanta, Georgia

FDA PRESENTATION

Review of Studies on Topiramate Use in Pregnancy and Risk of Oral Clefts and Major Congenital Malformations	**Julia Ju, Pharm.D., Ph.D.** Pharmacoepidemiologist Division of Epidemiology I Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology (OSE) CDER, FDA
Risk Management Options for Phentermine/Topiramate	**Joyce Weaver, Pharm.D.** Senior Drug Risk Management Analyst

	Division of Risk Management Office of Medication Error Prevention and Risk Management (OMEPRM) OSE, CDER, FDA
SPONSOR PRESENTATION	**Vivus, Inc.**
Qnexa REMS	**Barbara Troupin, M.D.** Senior Director, Global Medical Affairs Vivus, Inc.

Clarifying Questions from the Committee

LUNCH

Open Public Hearing Session

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Advisory Committee:

1. Discuss your interpretation of the available data presented regarding teratogenicity of topiramate, including whether the data indicate an increase in the risk for oral clefs.

   Committee Discussion: *There was a general consensus from the committee that the data indicate an increase in the risk for oral clefs. However, it was difficult for the committee to discern whether the level of risk from the proposed dose of Qnexa (phentermine/topiramate) for obesity treatment would be comparable to that observed in the use of topiramate as a single-agent for other indications at higher doses. The committee noted that obesity in and of itself poses risks to the fetus. The committee suggested that additional methods for detecting birth defects may need to be implemented to further study the risk of oral clefs and other birth defects. Please see the transcript for details of the committee's discussion.*

2. Discuss the potential strengths and weaknesses of the proposed teratogenicity risk management strategy for phentermine/topiramate (PHEN/TPM).

   Committee Discussion: *The committee agreed that one of the strengths of the proposed risk management strategy is the frequent education and reinforcement of the information for both patients and providers. The committee also noted that provider certification may be more successful than provider education. The committee expressed significant concern regarding the sponsor's proposed use of a mail-order pharmacy as the sole distribution method, noting reliability concerns regarding timeliness of refills and insurance coverage. However, some*

committee members also noted that the pharmacy mail-order system may facilitate the collection of additional data from patients regarding birth defects.

The committee was also concerned that patients may not have the resources to consistently purchase pregnancy kits for monthly testing and contraceptive medications to prevent unplanned pregnancies. Additionally, the committee was concerned that the complexity of the REMS may result in patients and healthcare providers opting to use the individual components that make up Qnexa (phentermine/topiramate) for obesity treatment and thus circumventing the REMS requirements. Lastly, several committee members suggested including an oral clef picture in the labeling to provide patients with a visual reminder and a better understanding of the potential for birth defects. Please see the transcript for details of the committee's discussion.

3. Taking into account the reported changes in antihypertensive therapy, discuss the clinical significance of the changes in blood pressure and heart rate in overweight and obese patients treated with PHEN/TPM versus placebo.

   Committee Discussion: *The committee agreed that there was an observed difference in heart rate and blood pressure between patients taking Qnexa versus placebo. However, due to the way the data was captured, it was difficult for the committee members to interpret these observations. Additionally, the committee noted that it is difficult to determine how much the changes in blood pressure and heart rate were related to the weight loss and how much were related to the medication. Several panel members stated that heart rate is a good biomarker of clinical outcome, even in healthier populations and this can be used to predict future risk or reduction in mortality, as is seen with beta-blockers, which lower heart rate whereas phentermine/topiramate increases heart rate. Due to the small number of subjects in the studies used to support this new drug application (NDA), it is difficult for the committee to fully estimate the risks that derived from the limited data of heart rate and blood pressure. Please see the transcript for details of the committee's discussion.*

4. Discuss whether the available data for PHEN/TPM warrant that a cardiovascular outcomes trial be conducted prior to approval.

   Committee Discussion: *The committee agreed that there is not enough data at this time to adequately assess the cardiovascular (CV) risk for phentermine/topiramate. The committee indicated that the extension Study 305 (safety trial) has several issues which limit its analysis. The committee stressed that there was a possibility of selection bias in the sites that were used to enroll patients and that the patients were not randomized after the first year of the trial. As a result, the data could not be compared to the data captured from the one-year trial (Study 303). Over the one year period, the difference in the observed effect on blood pressure between patients on drug versus those on placebo was attenuated; however, the difference in heart rate persisted over time. The observed high-density lipoprotein (HDL) and triglyceride (TG) improved in patients on the drug versus those in the placebo group over the course of the trial but most panel members noted that low-density lipoprotein (LDL) changes are a better indicator of cardiovascular risk. Some panel members expressed reservations regarding a requirement for a CV trial to be conducted post-approval and*

stated that they would also support the idea of the CV trial being started prior to approval to make sure that the data needed to assess CV risk or benefit is available as soon as possible after approval of the drug. Please see the transcript for details of the committee's discussion.

5. Considering all the available data included in the application and today's discussions, does the overall benefit-risk assessment of PHEN/TPM support its approval for the treatment of obesity in individuals with a body mass index (BMI) $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with weight-related co-morbidities? (VOTING)

   YES: 20 **NO: 2**

   a. If you voted "Yes" in question #5, please provide your rationale and comment on the approach to post-approval risk management.

   Committee Discussion: *The committee members who voted "YES" in question #5 noted that obesity is a disease for which there are inadequate treatment methods and that phentermine/topiramate (Qnexa) was shown to be effective in treating obesity with minimal adverse effects. However, they supported the requirement for a post-approval long-term cardiovascular (CV) safety trial which should be conducted expeditiously. It was noted that the sponsor should be held accountable for conducting and completing this CV trial. Additionally, these committee members agreed that the phentermine/topiramate REMS should capture additional data on long-term adverse events such as heart rate, psychological, cognitive functions, and birth defects. Several members highlighted the need to require treating physicians to be certified prior to treating patients with this agent and that the same requirement should be instituted for dispensing pharmacies. Lastly, the FDA was also urged to require the sponsor to continue to re-analyze any available data regarding reproductive outcomes such as birth defects. Please see the transcript for details of the committee's discussion.*

   b. If you voted "No" in question #5, please provide your rationale and comment on what additional clinical data would be required to support approval.

   Committee Discussion: *One committee member who voted "NO" in question #5 commented that it would be a mistake for the Agency to approve this drug at this point using only surrogate outcomes, and indicated that the sponsor should be required to expeditiously conduct a trial to further capture data in higher risk patients. Please see the transcript for details of the committee's discussion.*

The meeting was adjourned at approximately 5:00 p.m.