

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22580Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022580

SUPPL #

HFD # 510

Trade Name Qsymia

Generic Name phentermine and topiramate extended-release capsules, for oral use, CIV

Applicant Name Vivus, Inc.

Approval Date, If Known 07/17/12

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020505 Topamax (topiramate) tablet

NDA# 020844 Topamax (topiramate) capsule

NDA# 011613 Ionamin (phentermine resin)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. OB-301 - To demonstrate that 2 different dose levels of VI-0521 results in weight loss that is greater than placebo and the single-agent PHEN and TPM constituents that compromise each dose

To evaluate the safety of 2 different doses of VI-0521 compared to placebo and the single-agent constituents

2. OB-302 - To evaluate the safety and efficacy of 2 doses of VI-0521 for the treatment of obesity in adults with a BMI ≥ 35 kg/m²

3. OB-303 - To evaluate the safety and efficacy of 2 doses of VI-0521 for the treatment of obesity in adults with ≥ 2 obesity-related, co-morbid conditions and to examine the effects of VI-0521 on obesity-related co-morbidities

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NONE OF THE 3 INVESTIGATIONS WERE PREVIOUSLY RELIED ON

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the

effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NONE OF THE 3 INVESTIGATIONS DUPLICATE THE RESULTS OF ANOTHER INVESTIGATION RELIED ON BY THE AGENCY

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. OB-301 - To demonstrate that 2 different dose levels of VI-0521 results in weight loss that is greater than placebo and the single-agent PHEN and TPM constituents that compromise each dose

To evaluate the safety of 2 different doses of VI-0521 compared to placebo and the single-agent constituents.

2. OB-302 - To evaluate the safety and efficacy of 2 doses of VI-0521 for the treatment of obesity in adults with a BMI ≥ 35 kg/m²

3. OB-303 - To evaluate the safety and efficacy of 2 doses of VI-0521 for the treatment of obesity in adults with ≥ 2 obesity-related, co-morbid conditions and to examine the effects of VI-0521 on obesity-related co-morbidities.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 068651 YES ! NO

! Explain:
FOR ALL 3 INVESTIGATIONS

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Pooja Dharia
Title: Regulatory Project Manager
Date: 07/11/12

Name of Office/Division Director signing form: Eric Colman
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

POOJA DHARIA
07/17/2012

ERIC C COLMAN
07/17/2012



DEBARMENT CERTIFICATION

Regarding Original NDA 22-580, QNEXA™ (phentermine/topiramate) controlled release capsules.

I, the undersigned, do here hereby certify that VIVUS, Inc. did not and will not use in any capacity the services of any person debarred under section 306 of the Food, Drug and Cosmetic Act in connection with this application.

A handwritten signature in black ink, appearing to read "Peter Tam", written over a horizontal line.

Peter Tam, M.B.A.
President

19 November 2009

Date

1.3 Administrative Documents

1.3.3 Debarment Certification

A debarment certification for NDA 22-580 is provided herein.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022580 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Qsymia Established/Proper Name: phentermine and topiramate extended-release capsules, for oral use, CIV Dosage Form: Capsule		Applicant: Vivus, Inc. Agent for Applicant (if applicable):
RPM: Pooja Dharia		Division: Division of Metabolism and Endocrinology Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Topamax (topiramate) NDA 20505 (100 mg, 200 mg, 50 mg oral tablets) NDA 20844 (15 mg, 25 mg oral capsules)</p> <p>Adipex-P (phentermine) ANDA 88023 (37.5 mg oral capsule) ANDA 85128 (37.5 mg oral tablet)</p> <p>Topamax Product Monograph 2007</p> <p>Ionamin (phentermine resin) NDA 11613</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Qsymia is a new combination of topirmate and phentermine.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input checked="" type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 07/17/12, CR 10/28/10
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	10/17/11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.
Version: 7/8/10

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 	10/17/11
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	7/17/2012
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	03/05/10, 05/15/12, 06/15/12 02/18/10, 04/16/12, 06/14/12
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 06/04/10, 02/10/12, <input checked="" type="checkbox"/> DRISK 10/1/10 <input checked="" type="checkbox"/> DDMAC 06/12/12, 06/14/12 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 05/25/10, 06/01/12
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	08/17/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 03/20/12
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Not a (b)(2) 07/17/12
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
<ul style="list-style-type: none"> Date reviewed by PeRC <u>03/07/12</u> If PeRC review not necessary, explain: _____ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	03/26/10, 07/19/11, 09/01/11, 04/06/12
❖ Internal memoranda, telecons, etc.	08/24/10, 10/28/10, 06/13/11, 09/08/11, 04/06/12

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 7/8/10

❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 08/20/10
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg 01/19/11, 04/27/11
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 07/22/09
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 05/02/07
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	12/19/11, 01/12/12, 03/21/12
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	July 15, 2010, February 22, 2012
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/28/10, 07/17/12 (3)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 10
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	10/27/10, 07/17/12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Medical Officer review: 10/27/10, page 28
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 06/02/10, 06/07/10, 06/09/10, 06/17/10, 06/18/10, 06/29/10, 07/15/11, 10/21/11, 12/21/11, 12/29/11, 01/13/12, 01/22/12 (2), 01/27/12, 03/15/12, 04/23/12, 05/22/12, 05/29/12, 06/01/12, 07/02/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable 08/10/10, 05/15/12
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	12/28/09, 08/09/10, 10/14/12, 07/17/12
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	10/27/10, 07/17/12
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None 10/12/10, 5/17/12, 07/17/12
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 06/29/10, 08/16/10, 08/17/10, 09/22/10, 09/8/11, 02/15/12, 03/14/12

⁵ Filing reviews should be filed with the discipline reviews.
Version: 7/8/10

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None 05/17/10, 09/27/10, 07/19/11, 10/14/11, 03/22/12
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None 08/30/10, 03/20/12, 06/07/12, 06/26/12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)		<input type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> None 10/01/10
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None 10/01/10, 03/22/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> No carc 11/09/10
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None 08/11/10 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None 06/09/10, 07/19/10, 10/05/10, 11/08/11, 03/12/12
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Acceptable: 06/09/10 CMC review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 10/05/10, 07/11/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.
Version: 7/8/10

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

POOJA DHARIA
07/18/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 17, 2012

FROM: Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products (DMEP)

TO: NDA 22580 – Vivus Pharmaceuticals
Qsymia (fixed-dose combination of phentermine and extended-release topiramate) capsules - 3.75/23 mg; 7.5/46 mg; 11.25/69 mg; and 15/92 mg

SUBJECT: Citizen Petition Seeking to Delay Approval of Vivus' NDA 22580

On July 11, 2012, FDA received a citizen petition (2012-P-0738) (dated July 9, 2012) from Joseph Dedvukaj requesting that we refrain from approving Vivus Inc.'s Section 505(b)(2) new drug application (NDA) for Qsymia (NDA 22580).¹ Qsymia is a fixed-dose combination of phentermine and extended-release topiramate for weight management. The PDUFA goal date on the Qsymia NDA is July 17, 2012, less than one week after the citizen petition was received by FDA.

Because the citizen petition requests action that could delay approval of a pending 505(b)(2) application, the petition is subject to section 505(q) of the Federal Food, Drug & Cosmetic (FD&C) Act.² Under section 505(q)(1)(A)(ii), FDA may not delay the approval of a 505(b)(2) or (j) application based on a request to take action relating to the application unless we determine, "upon reviewing the petition, that a delay is necessary to protect the public health." Our guidance on 505(q) petitions states that, unless the petition may be summarily denied because we conclude that the primary purpose of the petition is to delay approval and it does not on its face raise valid scientific or regulatory issues, we are to determine whether a delay is necessary to protect the public health based on our preliminary evaluation of the issues raised in the petition.³ We have now completed that evaluation and, as summarized in this memorandum, determined that a delay of approval of NDA 22580 is not necessary to protect the public health.

¹ The petition was initially submitted on July 11, 2012, but lacked the complete certification required under section 505(q)(1)(H) of the Federal Food, Drug and Cosmetic Act (FD&C Act). ORP contacted the petitioner on July 12, 2012 to inform him of this deficiency (as well as the petition's lack of an Environmental Impact Statement) and to notify him that unless the certification deficiency was cured, the petition would be unreviewable under the statute. The petition was resubmitted with the proper certification on July 17, 2012 (2012-P-0764).

² Guidance for Industry on *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug and Cosmetic Act* (June 2011) at 4-5.

³ Id. at 7-8.

We are not issuing a petition response prior to approval, but will respond to the petition within the statutory timeframe.

I. Background

Qsymia is a fixed-dose combination of phentermine and extended-release topiramate. Both phentermine and topiramate are approved as single-ingredient drug products for other indications, and at higher doses than are present in Qsymia.

Phentermine, a sympathomimetic, was approved in 1959 for the treatment of obesity. Since 1973, it has been indicated for short-term use only. The approved doses for phentermine are up to 37.5 mg/day.

Topiramate, an inhibitor of carbonic anhydrase, was approved in 1996 for the treatment of seizures and in 2004 for the prevention of migraine headache. The approved doses for topiramate are up to 400 mg/day for seizures and up to 100 mg/day for migraine prophylaxis.

II. Analysis

A. Teratogenicity

Petitioner argues that there has been insufficient assessment of teratogenicity associated with the topiramate in Qsymia, and final results from the Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS) are necessary to determine whether Qsymia is safe.

Final results from FORTRESS, a retrospective cohort study, are expected in approximately one year. However, the Vivus NDA is supported by other teratogenicity data, including an observational study conducted by the Centers for Disease Control (CDC) and the Slone Epidemiology Center at Boston University, and an observational study published by Wolters Kluwer. The body of evidence from these sources is sufficient to make an assessment of topiramate's teratogenic risk and how it affects Qsymia's benefit-risk profile. This evidence is discussed at length in Dr. Roberts' review⁴ and my review.⁵

B. Cardiovascular Risks

Petitioner notes that Qsymia is associated with an increase in resting heart rate, and argues that there has been inadequate assessment of the cardiovascular risks of Qsymia in obese patients with cardiovascular co-morbidities.

⁴ Clinical Review: Complete Response Submission, Dr. Mary Dunne Roberts (Roberts Review), Section 7.6.2 (July 17, 2012).

⁵ Deputy Division Director Summary Review, Dr. Eric Colman, Section 7 -- Teratogenicity (July 17, 2012).

FDA's analysis of the data regarding Qsymia's effect on heart rate and cardiovascular risk is described in detail in Dr. Roberts' review.⁶ As discussed there, while Qsymia is associated with a small mean increase in heart rate, it also reduces blood pressure such that the change in the rate-pressure product – a surrogate of myocardial oxygen demand – is similar for Qsymia and placebo-treated subjects. In addition, analyses of cardiovascular-related adverse event data from the Qsymia phase 2 and 3 clinical trials, while limited in scope, do not raise concerns of excessive risk.

Further, Qsymia's labeling will recommend that prescribers monitor heart rate in all patients, especially those with cardiac or cerebrovascular disease. The labeling will also state that Qsymia has not been studied in patients with advanced or unstable cardiovascular and cerebrovascular disease, and therefore its use is not recommended in those patients.

The sponsor will be required to conduct a post-approval randomized, double-blind, placebo-controlled trial to prospectively evaluate the long-term effect of Qsymia on the incidence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in obese subjects with cardiovascular disease or multiple cardiovascular risk factors.

C. Risk Evaluation and Mitigation Strategy

Petitioner argues that there is insufficient information to show that the proposed Risk Evaluation and Mitigation Strategy (REMS) for Qsymia will adequately protect against fetal exposure to topiramate, a teratogen. Petitioner also contends that a REMS is unlikely to be effective because single-ingredient topiramate and phentermine products are available without a REMS, and suggests that approval of Qsymia with a REMS will encourage off-label combination use of the single-ingredient products for weight loss.

The decision that a REMS is necessary to ensure the benefits outweigh the risks for a particular drug is a fact-specific inquiry that requires consideration of the following factors: (1) the estimated size of the population likely to use the drug, (2) the seriousness of the disease or condition to be treated, (3) the expected benefit of the drug with respect to the disease or condition, (4) the expected or actual duration of treatment with the drug, (5) the seriousness of known/potential adverse events that may be related to the drug and the background incidence of these events in the population likely to use the drug, and (6) whether the drug is a new molecular entity.

Based on its consideration of these factors, FDA has determined that a REMS that includes elements to assure safe use is necessary for Qsymia to ensure that the benefits of the drug outweigh the risk of congenital malformations (specifically orofacial clefts) in infants exposed to Qsymia during the first trimester of pregnancy. The goal of the REMS is to inform prescribers and female patients of reproductive potential about 1) the increased risk of congenital

⁶ See Roberts Review, Section 7.3.5.

malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy, 2) the importance of pregnancy prevention for females of reproductive potential receiving Qsymia, and 3) the need to discontinue Qsymia immediately if pregnancy occurs.

The Agency has tools at its disposal to ensure that the REMS for Qsymia is meeting its goals and mitigating the risk of teratogenicity posed by Qsymia. The REMS requires that assessments be submitted to FDA at 6 months and 12 months after approval, and annually thereafter. If, upon review of the required assessments, FDA determines that changes to the REMS are necessary to ensure that the benefits of the drug outweigh the risks, it can require modification of the REMS.

To the extent that petitioner is suggesting that approval of Qsymia will affect the safety profile of topiramate as a single-ingredient drug product, delaying approval of Qsymia would not be an appropriate remedy. Should the safety profile of topiramate as a single-ingredient drug product change following approval of Qsymia, FDA can address any related safety concerns using its range of tools and authorities under the FD&C Act. Moreover, to the extent that healthcare providers likely to prescribe the single-ingredient drug products for weight loss are part of the target group for training and education under the Qsymia REMS, they will be provided information under the REMS regarding the risk of orofacial clefts. Accordingly, the approval of Qsymia with a REMS is designed to enhance patient safety, rather than to undermine it.

Finally, the sponsor will be required to conduct a prospective cohort study to determine the frequency of pregnancy in Qsymia patients, and compare the risk of oral clefts and major congenital malformations in the offspring of women exposed to Qsymia during pregnancy with women who were not so exposed. The sponsor also will be required to conduct an annual drug use study for 7 years. The agency will carefully monitor this information and any other safety reports and usage patterns, and take additional regulatory actions as appropriate.

III. Conclusion

As discussed in detail in my review and that of Dr. Mary Roberts, DMEP has concluded that the benefits of Qsymia outweigh its risks, and that it should be approved. Both active components of the combination, phentermine and topiramate, are currently approved and marketed at higher doses than those in Qsymia. DMEP believes that the REMS designed for Qsymia will adequately mitigate the teratogenic risks associated with its use for chronic weight management. For the foregoing reasons, the arguments raised by the petitioner do not change these conclusions.

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/s/

ERIC C COLMAN
07/17/2012

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/s/

CAROL A HOLQUIST
06/15/2012



NDA 022580

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

VIVUS, Inc.
1172 Castro Street
Mountain View, CA 94040

Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for phentermine and topiramate extended-release capsules, 3.75 mg /23mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg. Please also refer to your complete Class 2 resubmission to this NDA, dated and received October 17, 2011.

We also refer to your correspondence dated and received May 31, 2012, requesting review of your proposed proprietary name, Qsymia. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your May 31, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Pooja Dharia at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

CAROL A HOLQUIST
06/15/2012

Dharia, Pooja

From: Dharia, Pooja
Sent: Thursday, June 14, 2012 1:39 PM
To: 'Malcolm McKay'
Subject: Qsymia information request 6/14/12

Attachments: QnexanonRespPredict_RFI_Stat 6-6-12 (2).doc

Hi Malcolm,

Please see attached for a statistical information request for the Qsymia label.



QnexanonRespPred
ict_RFI_Stat 6...

Thanks,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Request for Information for Qsymia's label: Predicting Week 52 weight loss non-responders from Week 12 results

We would like to include the following statement (or similar statement) in Part 2 (Dosage and Administration) of the label: “If after 3 months of treatment with a daily dose of Tradename 7.5 mg/46 mg a patient has not lost at least (*criterion level %*) of baseline body weight, discontinue Tradename (*Table reference*).” The table reference will point to a table in Part 14, showing the sensitivity and specificity of the criterion level of weight loss at week 12.

You identified a criterion level of 3% weight loss at week 12. We calculated a preliminary evaluation of sensitivity and specificity (Table 1) for 1 year cohort of phase 3 studies. We request that you evaluate the sensitivity and specificity further, in order to select a criterion level for the label. We request that the evaluation include the following:

1. Data from the 7.5/46 mg dose of Study 303.
2. Use the 5% responder endpoint at week 52, with the MITT/LOCF database.
3. Use a Yes/No responder endpoint at week 12 for the predictor variable (MITT/LOCF).
4. Evaluate criterion levels of 3%, 4% and 5% for the Yes/No responder endpoint at week 12. Other criterion levels can also be included.
5. Calculate sensitivity and specificity, defined with reference to correctly identifying a 5% non-responder at week 52, based on being classified as a (*criterion-level %*) non-responder at week 12.

Table 1. For Phen/Tpm 7.5/46, based on a criterion of 3% at week 12:

	Correctly classified at week 56	Incorrectly classified at week 56	Total
Week 12 non-responder	108 (a non-responder at week 56)	32 (a responder at week 56)	140
Week 12 responder	271 (a responder at week 56)	77 (a non-responder at week 56)	348
Sensitivity: (# non-responders at week 56 correctly predicted by being <u>classified as a non-responder at week 12</u>) (# week 12 non-responders)	108/	108/185 (108+77)	58.4%
Specificity: (# responders at week 56 correctly predicted by being <u>classified as a responder at week 12</u>) (#week 12 responders)	271/	271/303 (271+32)	89.4%

We also request that a similar evaluation be conducted for the statement that (b) (4)

[Redacted]

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/s/

POOJA DHARIA
06/14/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING DATE: May 25, 2012
TIME: 1:00 pm – 2:00 pm
LOCATION: WO 22 Room 4396
APPLICATION: NDA 22580
DRUG NAME: Phentermine/ Topiramate Extended-Release Capsules
TYPE OF MEETING: Proprietary Name review teleconference

APPLICANT: Vivus, Inc.

MEETING CHAIR: Kellie Taylor, Deputy Director, DMEPA

MEETING RECORDER: Ermias Zerislassie, Safety Regulatory Project Manager, OSE

FDA ATTENDEES:

Kellie Taylor, Deputy Director, DMEPA, OSE
Kevin Wright, Safety Evaluator, DMEPA, OSE
Ermias Zerislassie, Safety Regulatory Project Manager, OSE
Susannah Hubert, OMPT/CDER/OMP/OPDP
James Dvorsky, OMPT/CDER/OMP/OPDP
Bryant Godfry, OMPT/CDER/OMP/OPDP
Marcy Kiester, OMPT/CDER/OMP/OPDP

SPONSOR ATTENDEES:

Robert Janosky, Director Commercial
Malcolm McKay, VP Regulatory
Michael Miller, SVP Commercial
Leland Wilson, CEO

Background:

DMEPA requested this teleconference to discuss identified concerns with proprietary name submission provided by the sponsor, (b) (4) and alternate submission (b) (4) and to discuss the regulatory path forward.

Discussion

OPDP objects to the proposed proprietary name "(b) (4)" because it (b) (4) (b) (4). The name (b) (4) accessed (b) (4) 5/22/12). The proposed indication for this drug is for the treatment of obesity, including weight loss and maintenance of weight loss. Weight loss goals are often discussed in terms of (b) (4). In the absence of (b) (4) the proposed name is misleading.

DMEPA informed sponsor that (b) (4) is not viable from a safety perspective. (b) (4) can be potentially confused with the name (b) (4) due to orthographic similarity and overlapping product characteristics.

Sponsor asked what they would have to do to demonstrate that the name (b) (4) poses a low safety risk. DMEPA responded with the following:

- The sponsor would have to provide usage numbers for (b) (4)
- Demonstrate the firm which formerly marketed (b) (4) is unable to re-enter market.
- Determine who owns (b) (4) trademark
- Reach out to vendors to remove (b) (4) from the various databases

Post-Meeting minutes

REGULATORY PATH FORWARD

- Sponsor will either amend their submission for (b) (4) with the information outlined by DMEPA or submit a formal withdrawal of the (b) (4) application and formally submit the new proposed trade name (and an alternate name).

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/s/

ERMIAS ZERISLASSIE
06/12/2012

KELLIE A TAYLOR
06/12/2012



NDA 022580

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Vivus, Inc.
1172 Castro Street
Mountain View, CA 94040

Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Phentermine and Topiramate Extended-release Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg. Please also refer to your complete Class 2 resubmission to this NDA, dated and received October 17, 2011.

We also refer to:

- Your proprietary name submission dated and received April 18, 2012, for the proposed proprietary name, (b)(4) as well as the alternate names (b)(4).
- Your May 8, 2012, teleconference with the Agency to discuss your request for review and preliminary findings for the proprietary name, (b)(4) as well as the alternate names (b)(4).

We acknowledge receipt of your May 9, 2012, correspondence, on May 9, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b)(4) as well as the alternate names (b)(4). This proposed proprietary name request is considered withdrawn as of May 9, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Pooja Dharia at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/15/2012

CDER/DRUP Consultation Response (Tracking No. 334)

Division Consult #	334
To	Pooja Dharia, Pharm.D. Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
From	Gerald Willett MD, Medical Officer, Division of Reproductive and Urologic Products (DRUP) through Lisa Soule, MD, Medical Team Leader and Audrey Gassman MD, Acting Deputy Division Director
Name of drug product	QNEXA® (phentermine/topiramate) extended-release capsules – NDA 022580
Class of drugs	Obesity
Sponsor	Vivus, Inc. 1172 Castro Street Mountain View, CA, 94040
Re:	Drug interactions with Oral Contraceptive (OC)
Date of consult request	May 10, 2012
Desired completion date	May 29, 2012

Background

This is the second consult from DMEP regarding QNEXA (phentermine/topiramate). A copy of the first consult is presented in the Appendix of this consult review. In this consult DMEP is requesting DRUP to provide labeling language that will provide healthcare providers and patients with information about the clinical significance of the drug-drug interactions (DDIs) between QNEXA and an oral contraceptive (norethindrone 1 mg/ ethinyl estradiol 35 mcg).

DMEP stated that the Applicant's proposed wording in the label regarding this DDI is as follows:

“Co-administration of multiple dose QNEXA 15 mg/92 mg once daily with a single oral contraceptive dose containing 35 µg ethinyl estradiol and 1 mg norethindrone decreased the ethinyl estradiol AUC by 16% and increased the norethindrone C_{max} and AUC by 22% and 16%, respectively, in obese otherwise healthy volunteers.”

DRUP response:

We suggest the following labeling comment after this DDI information:

“Although this study did not specifically address the impact of the interaction on contraceptive efficacy, an increased risk of pregnancy is not anticipated. The primary

determinant of contraceptive efficacy is the progestin component of the combination oral contraceptive, so higher exposure to the progestin would not be expected to be deleterious.

However, irregular spotting may occur more frequently due to both the increased exposure to the progestin and lower exposure to the estrogen, which tends to stabilize the endometrium. Patients should be informed not to discontinue their combination oral contraceptive if spotting occurs, but to notify their health care provider if the spotting is troubling to them.”

DMEP also asked for DRUP’s comment in regard to acceptable birth control methods in light of typical use of birth control and the teratogenicity of QNEXA. Their proposal presents 3 different options (shown below):

Option 1



DRUP Comment:

We recommend the following wording for Option 1; we propose deleting [redacted] (b) (5) and adding the option of a progestin implant (i.e., Implanon or Nexplanon), which is grouped with the most effective contraceptive methods in COC class labeling:

Highly Effective Methods to Use Alone

- *Intrauterine device (IUD) or system (IUS)*
 - *Copper IUD*
 - *Levonorgestrel-releasing IUS*
- *Progestin implant*
- *Tubal sterilization*
- *Male partner’s vasectomy*

Option 2

(b) (5)

DRUP Comment:

We recommend the following minor revisions to Option 2:

Acceptable Methods to Use in Combination

<i>Choose One First Method</i>		<i>Choose One Second Method</i>
<i>Hormonal Contraception</i> <ul style="list-style-type: none">• <i>Estrogen and progestin</i><ul style="list-style-type: none">○ <i>Oral</i>○ <i>Transdermal patch</i>○ <i>Vaginal ring</i>• <i>Progestin only</i><ul style="list-style-type: none">○ <i>Oral</i>○ <i>Injection</i>	+	<i>Barrier Method</i> <ul style="list-style-type: none">• <i>Diaphragm (with spermicide)</i>• <i>Cervical cap (with spermicide)</i>• <i>Male condom (with or without spermicide)</i>

Option 3

(b) (5)

DRUP Comment:

We recommend the following minor revisions to Option 3:

Acceptable Methods to Use in Combination

<i>Choose One First Method</i>		<i>Second Method</i>
<i>Barrier Method</i> <ul style="list-style-type: none">• <i>Diaphragm (with spermicide)</i>• <i>Cervical cap (with spermicide)</i>	+	<i>Barrier Method</i> <i>Male condom (with or without spermicide)</i>

Appendix

First DRUP consult for QNEXA (phentermine/topiramate)

Background

DMEP is currently reviewing a combination drug product for the treatment of obesity. This product consists of immediate-release phentermine hydrochloride beads and modified-release topiramate beads. The trade name is QNEXA.

There are 4 dosage strengths for QNEXA. Titration is recommended upon initiation of the drug. The dosages are 3.75/23 mg, 7.5/46 mg, 11.25/69 mg and 15/92 mg. The 7.5/46 mg dose is the recommended dose for weight loss but can be titrated to the 15/92 mg level if weight loss goals have not been achieved after 3-4 months.

DMEP indicated in its consult request that first trimester exposure to topiramate has been associated with an increased risk of oral clefts (based on pre-clinical and observational data). This product will therefore be classified as Pregnancy Category X (contraindicated in pregnancy). Reproductive-age women taking this product will therefore require effective contraception.

DMEP also provided DRUP with information regarding a drug-drug interaction (DDI) study that evaluated QNEXA with an oral contraceptive containing 1 mg norethindrone (NE) and 35 mcg ethinyl estradiol (EE). The DDI study number was OB-108. The study report was submitted with the original NDA on 12/28/2009.

In Study OB-108 the combination oral contraceptive (COC) was Nortrel (norethindrone 1 mg; ethinyl estradiol 35 mcg), which is manufactured by Barr Laboratories, Inc. The study evaluated women whose body mass was ≥ 27 but ≤ 35 kg/m². The pharmacokinetics testing was based on the following schedule:

Study Day(s)	COC administered	QNEXA administered	PK testing
1	NE 1 mg/ EE 35 mcg x 1		X
3-6		3.75/23 mg once daily	
7-10		7.5/46 mg once daily	
11-14		11.25/69 mg once daily	
15-30		15/92 mg once daily	X (Day 29)
29	NE 1 mg/ EE 35 mcg x 1		X

The Applicant's pharmacokinetic findings for the COC in Study OB-18 were the following:

Test		Change in EE
C _{max}	Maximum observed drug concentration	Decrease by 8%
AUC _{0-inf}	Area under the drug concentration-time curve from time zero to infinity	Decrease by 16%

Test		Change in NE
C _{max}	Maximum observed drug concentration	Increase by 22%
AUC _{0-inf}	Area under the drug concentration-time curve from time zero to infinity	Increase by 16%

The Applicant reported no serious adverse events in Study OB-108 and no subjects were discontinued due to adverse events. Adverse events reported by four or more subjects (of 20 in this study) include constipation, decreased appetite, dry eye, dry mouth, headache, insomnia and paraesthesia/hypoaesthesia. These adverse events are similar to those reported in the proposed QNEXA drug label.

The most commonly reported adverse reactions reported in the label for QNEXA include:

Adverse Reaction	%
Paresthesia	17
Dry mouth	16.6
Constipation	15.1

The only gynecologic adverse event noted in the label that occurred more commonly compared to placebo was dysmenorrhea (0.8% with QNEXA compared to 0.2% for placebo).

Medical Officer's Comment:

Twenty subjects were enrolled in this DDI study and the study duration was a single month. The adverse events in the DDI study were similar to the adverse events listed in the QNEXA label. However, the concurrent exposure to both QNEXA and the COC was minimal because the subjects were only exposed to 2 doses of COC (Days 1 & 29).

Dr. Mary Roberts also provided a safety set table from 4 separate studies in the Integrated Summary of Safety showing menstrual disorder information for use of QNEXA. Unfortunately this data was not analyzed by the Applicant according to concurrent use of COCs which limits its usefulness.

The specific consultation questions and DRUP responses are:

Consultation Questions:

A drug-drug interaction study was conducted with the FDC (15 mg/92 mg) and an oral contraceptive containing 1 mg norethindrone and 35 mcg ethinyl estradiol. The combination resulted in a 16% increase in AUC and 22% increase in C_{max} of the progestin component, and a 16% decrease in AUC and 8% decrease in C_{max} of the estrogen component. It is unclear to us as to how this may impact a woman's fertility. We are attempting to come up with language for the PI and REMS as to what would constitute effective contraception in females of reproductive potential taking the FDC.

Do you consider the PK data to be clinically meaningful, i.e., would you expect there to be a decrease in the contraceptive effect of OCP when co-administered with QNEXA?

Consult response:

Based on the decreased AUC and Cmax for EE (16% and 8%) and the increased AUC and Cmax for NE (16% and 22%, respectively) this reviewer does not anticipate that there will be significant impact on contraceptive efficacy. Much of the contraceptive benefit for COCs relates to the progestin component. Increasing the NE exposure could theoretically improve efficacy if it resulted in more luteinizing hormone inhibition or alteration of cervical mucus.

From a clinical standpoint, the main alteration that theoretically may be induced by slightly increasing progestin exposure and slightly decreasing estrogen exposure would be related to more irregular spotting/bleeding because the estrogen component tends to stabilize the endometrial lining.

Proposed Labeling and REMS:

The proposed label for the FDC states:

Contraception

Females of reproductive potential should use effective contraception during FDC therapy.

(b) (4)

The proposed REMS states:

(b) (4)

Additional Comments:

Although efficacy issues based on the PK findings are not anticipated, I would not object if the label and REMS recommended use of additional non-hormonal methods of contraception based on the concern for topiramate teratogenicity. Based on work by James Trussell at Princeton, COCs and progestin-only oral contraceptives as a group can have a pregnancy rate of up to 9% in typical use.

DMEP also provided an excerpt from the current TOPAMAX label. There is a statement in the approved TOPAMAX label (Sections 7.3 and 12.3) that reads:

“The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.”

DRUP finds this labeling misleading. The labeling appears to imply that there is a correlation between decreased contraceptive efficacy and increased breakthrough bleeding. We are not aware of evidence demonstrating this. On the other hand, many women on COCs will have breakthrough bleeding, particularly in the initial months of use, and this is not a signal of impaired contraceptive efficacy.

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/s/

GERALD D WILLETT
05/22/2012

LISA M SOULE
05/22/2012

AUDREY L GASSMAN
05/22/2012

CDER/DRUP Consultation Response (Tracking No. 327)

Division Consult #	327
To	Pooja Dharia, Pharm.D. Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
From	Gerald Willett MD, Medical Officer, Division of Reproductive and Urologic Products (DRUP) through Lisa Soule, MD, Medical Team Leader and Audrey Gassman MD, Acting Deputy Division Director
Name of drug product	QNEXA® (phentermine/topiramate) extended-release capsules – NDA 022580
Class of drugs	Obesity
Sponsor	Vivus, Inc. 1172 Castro Street Mountain View, CA, 94040
Re:	Drug interactions with Oral Contraceptive (OC)
Date of consult request	April 17, 2012
Desired completion date	April 25, 2012

Background

DMEP is currently reviewing a combination drug product for the treatment of obesity. This product consists of immediate-release phentermine hydrochloride beads and modified-release topiramate beads. The trade name is QNEXA.

There are 4 dosage strengths for QNEXA. Titration is recommended upon initiation of the drug. The dosages are 3.75/23 mg, 7.5/46 mg, 11.25/69 mg and 15/92 mg. The 7.5/46 mg dose is the recommended dose for weight loss but can be titrated to the 15/92 mg level if weight loss goals have not been achieved after 3-4 months.

DMEP indicated in its consult request that first trimester exposure to topiramate has been associated with an increased risk of oral clefts (based on pre-clinical and observational data). This product will therefore be classified as Pregnancy Category X (contraindicated in pregnancy). Reproductive-age women taking this product will therefore require effective contraception.

DMEP also provided DRUP with information regarding a drug-drug interaction (DDI) study that evaluated QNEXA with an oral contraceptive containing 1 mg norethindrone (NE) and 35 mcg ethinyl estradiol (EE). The DDI study number was OB-108. The study report was submitted with the original NDA on 12/28/2009.

In Study OB-108 the combination oral contraceptive (COC) was Nortrel (norethindrone 1 mg; ethinyl estradiol 35 mcg), which is manufactured by Barr Laboratories, Inc. The

study evaluated women whose body mass was ≥ 27 but ≤ 35 kg/m². The pharmacokinetics testing was based on the following schedule:

Study Day(s)	COC administered	QNEXA administered	PK testing
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29	NE 1 mg/ EE 35 mcg x 1		X

The Applicant's pharmacokinetic findings for the COC in Study OB-18 were the following:

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Test		Change in NE
C _{max}	Maximum observed drug concentration	Increase by 22%
AUC _{0-inf}	Area under the drug concentration-time curve from time zero to infinity	Increase by 16%

The Applicant reported no serious adverse events in Study OB-108 and no subjects were discontinued due to adverse events. Adverse events reported by four or more subjects (of 20 in this study) include constipation, decreased appetite, dry eye, dry mouth, headache, insomnia and paraesthesia/hypoaesthesia. These adverse events are similar to those reported in the proposed QNEXA drug label.

The most commonly reported adverse reactions reported in the label for QNEXA include:

Adverse Reaction	%
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Constipation	15.1

The only gynecologic adverse event noted in the label that occurred more commonly compared to placebo was dysmenorrhea (0.8% with QNEXA compared to 0.2% for placebo).

Medical Officer's Comment:

Twenty subjects were enrolled in this DDI study and the study duration was a single month. The adverse events in the DDI study were similar to the adverse events listed in the QNEXA label. However, the concurrent exposure to both QNEXA and the COC was minimal because the subjects were only exposed to 2 doses of COC (Days 1 & 29).

Dr. Mary Roberts also provided a safety set table from 4 separate studies in the Integrated Summary of Safety showing menstrual disorder information for use of QNEXA. Unfortunately this data was not analyzed by the Applicant according to concurrent use of COCs which limits its usefulness.

The specific consultation questions and DRUP responses are:

Consultation Questions:

A drug-drug interaction study was conducted with the FDC (15 mg/92 mg) and an oral contraceptive containing 1 mg norethindrone and 35 mcg ethinyl estradiol. The combination resulted in a 16% increase in AUC and 22% increase in Cmax of the progestin component, and a 16% decrease in AUC and 8% decrease in Cmax of the estrogen component. It is unclear to us as to how this may impact a woman's fertility. We are attempting to come up with language for the PI and REMS as to what would constitute effective contraception in females of reproductive potential taking the FDC.

Do you consider the PK data to be clinically meaningful, i.e., would you expect there to be a decrease in the contraceptive effect of OCP when co-administered with QNEXA?

Consult response:

Based on the decreased AUC and Cmax for EE (16% and 8%) and the increased AUC and Cmax for NE (16% and 22%, respectively) this reviewer does not anticipate that there will be significant impact on contraceptive efficacy. Much of the contraceptive benefit for COCs relates to the progestin component. Increasing the NE exposure could theoretically improve efficacy if it resulted in more luteinizing hormone inhibition or alteration of cervical mucus.

From a clinical standpoint, the main alteration that theoretically may be induced by slightly increasing progestin exposure and slightly decreasing estrogen exposure would be related to more irregular spotting/bleeding because the estrogen component tends to stabilize the endometrial lining.

Proposed Labeling and REMS:

The proposed label for the FDC states:

Contraception

Females of reproductive potential should use effective contraception during FDC therapy.



The proposed REMS states:

Additional Comments:

Although efficacy issues based on the PK findings are not anticipated, I would not object if the label and REMS recommended use of additional non-hormonal methods of contraception based on the concern for topiramate teratogenicity. Based on work by James Trussell at Princeton, COCs and progestin-only oral contraceptives as a group can have a pregnancy rate of up to 9% in typical use.

DMEP also provided an excerpt from the current TOPAMAX label. There is a statement in the approved TOPAMAX label (Sections 7.3 and 12.3) that reads:

“The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.”

DRUP finds this labeling misleading. The labeling appears to imply that there is a correlation between decreased contraceptive efficacy and increased breakthrough bleeding. We are not aware of evidence demonstrating this. On the other hand, many women on COCs will have breakthrough bleeding, particularly in the initial months of use, and this is not a signal of impaired contraceptive efficacy.

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/s/

GERALD D WILLETT
04/23/2012

LISA M SOULE
04/23/2012

AUDREY L GASSMAN
04/23/2012

Dharia, Pooja

From: Dharia, Pooja
Sent: Tuesday, April 17, 2012 2:55 PM
To: 'Malcolm McKay'
Subject: Qnexa information request 4/17/12

Hi Malcolm,

In the rationale sent with the label on April 3, 2012, you stated "Adverse events associated with dose withdrawal were assessed comprehensively, and no signal for any additional events was observed."

Please provide this analysis of adverse events during the first month off study drug in subjects who discontinued study drug but remained on study grouped by treatment, SOC and preferred term.

Thanks,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Dharia, Pooja

From: Egan, Amy
Sent: Monday, April 16, 2012 3:29 PM
To: Davis, Daniel; Nguyen, Christine; Gassman, Audrey
Cc: Colman, Eric C; Best, Jeanine A; Tassinari, Melissa; Roberts, Mary; Dharia, Pooja; Hai, Mehreen; Weaver, Joyce; LaCivita, Cynthia
Subject: Question regarding the efficacy of OCP
Attachments: Picture (Enhanced Metafile)

Dear DRUP colleagues,

DMEP is reviewing a NDA for a weight loss product which is a fixed-dose combination (FDC) of phentermine and topiramate. First trimester exposure to topiramate has been associated with an increased risk of oral clefts, based on pre-clinical and observational data. The FDC of phentermine/topiramate will be a Category X, and will be contraindicated in pregnancy.

A drug-drug interaction study was conducted with the FDC (15 mg/92 mg) and an oral contraceptive containing 1 mg norethindrone and 35 mcg ethinyl estradiol. The combination resulted in a 16% increase in AUC and 22% increase in Cmax of the progestin component, and a 16% decrease in AUC and 8% decrease in Cmax of the estrogen component. It is unclear to us as to how this may impact a woman's fertility. We are attempting to come up with language for the PI and REMS as to what would constitute effective contraception in females of reproductive potential taking the FDC.

The proposed label for the FDC states:

Contraception

Females of reproductive potential should use effective contraception during FDC therapy.

(b) (4)

The proposed REMS states:

(b) (4)

Complicating all of this of course is the question of whether OCP's are equally effective in obese or overweight subjects as in normal weight subjects. Also, the magnitude of weight loss seen with this FDC may actually improve fertility.

We don't want to overstate the clinical meaning of the PK data in the product label or REMS, nor do we want to assume a lack of clinical meaning and misguide prescribers and patients and thereby potentially risk fetal

exposures. Our question to you is - Do you consider the PK data to be clinically meaningful, i.e., would you expect there to be a decrease in the contraceptive effect of OCP when co-administered with FDC?

Thanks for your help. If you have any questions, please feel free to call me at 301-796-2179.

Amy

As an FYI - the current topiramate label notes the following PK interaction with OCP (note that higher doses of topiramate than what are in the FDC were used in these studies):

7.3 Oral Contraceptives

Exposure to ethinyl estradiol was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when TOPAMAX® was given as adjunctive therapy in patients taking valproic acid. However, norethindrone exposure was not significantly affected. In another pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX®, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding [see [Clinical Pharmacology \(12.3\)](#)].

12.3 Pharmacokinetics

Oral Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX®, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose-dependent decrease in EE exposure for doses between 200 and 800 mg/day, there was no significant dose-dependent change in EE exposure for doses of 50 to 200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding [see [Drug Interactions \(7.3\)](#)].

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/s/

POOJA DHARIA
04/17/2012



NDA 022580

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your October 17, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate extended-release) capsule. As previously conveyed, this is a complete, class 2 response to our October 28, 2010, action letter.

On April 4, 2012, we received your April 3, 2012, solicited major amendment to this application. This submission included initial drafts of all of your proposed REMS materials. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **July 17, 2012**.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

POOJA DHARIA
04/06/2012



NDA 022580

MEETING MINUTES

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for QNEXA (phentermine/topiramate) Extended Release Capsule.

We also refer to the meeting between representatives of your firm and FDA on March 21, 2012. The purpose of the meeting was to continue to discuss the proposed REMS.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: Wednesday March 21, 2012 3:00 – 4:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: NDA 022580
Product Name: QNEXA (phentermine/topiramate)
Extended Release Capsule
Indication: Obesity
Sponsor/Applicant Name: Vivus, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy G. Egan, M.D., M.P.H.	Deputy Director for Safety
Mary Roberts, M.D.	Clinical Reviewer
Pooja Dharia, Pharm.D.	Regulatory Project Manager
Mehreen Hai, Ph.D.	Safety Regulatory Project Manager

Office of Surveillance and Epidemiology

Diane Wysowski, Ph.D.	Team Leader, Division of Epidemiology I
Joyce Weaver, Pharm.D.	Senior Risk Management Analyst, DRISK
Cynthia LaCivita, Pharm.D.	Risk Management Analyst Team Leader, DRISK
Claudia Karwoski, Pharm.D.	Director, DRISK

NDA 022580
Meeting Minutes
March 21, 2012

Pediatric and Maternal Health Staff

Jeanine Best, MSN, RN, PNP Senior Clinical Analyst

SPONSOR ATTENDEES

Wesley Day, Ph.D.	V.P. Clinical Development
Malcolm McKay, Ph.D.	V.P. Regulatory Affairs and Corporate Compliance
Michael P. Miller, M.B.A.	SVP, Chief Commercial Officer
Craig Peterson, M.S.	Senior Director, Clinical Development

(b) (6)

Peter Tam, M.B.A.	President
Barbara Troupin, M.D., M.B.A.	Sr. Director Medical Affairs

1.0 BACKGROUND

Qnexa (phentermine/topiramate) is a combination of two marketed products, phentermine and topiramate, with a proposed indication for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). The proposed doses for marketing are three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg.

A Complete Response letter was issued on October 28, 2010. Vivus submitted the complete response to this letter on October 17, 2011.

The purpose of this meeting is to discuss additional comments regarding the Risk Evaluation and Mitigation Strategies (REMS), Prescribing Information, and Pregnancy Surveillance Program.

2.0 DISCUSSION

FDA briefly summarized the PMRs that would be required should Qnexa be approved. The division will e-mail the details of the PMRs to Vivus by the end of the week. Vivus will need to submit, via e-mail, the requested timelines for final protocol submission, study completion, and study report submission for each PMR. FDA reminded Vivus that a protocol is considered final when FDA and the sponsor have reached agreement on the protocol. Vivus was advised to factor in sufficient time for FDA review and revision of protocols in their proposed timelines.

FDA began the meeting by stressing the importance of submitting near-finalized REMS materials for review. FDA also noted that meeting the PDUFA goal date of April 17th will be a challenge, as all REMS materials will have to be reviewed and finalized with multiple levels of clearance. Vivus will be submitting all REMS materials by March 30th (see attachment).

The sponsor's questions are repeated below, followed by the meeting discussion in *italics*:

1. The FDA has proposed serial redistribution of the complete DHCP letter at launch, 6, 12 and 24 months directly to the entire universe of potential prescribers as well as by medical societies, potentially exposing physicians to 8 identical DHCP letters within the first 2 years. VIVUS is concerned that this extent of duplicate messaging may lessen program effectiveness compared to the Sponsor's more focused proposal of (b) (4)

(2) repeated, risk messaging at 6, 12, and 24 months directed to documented Qnexa prescribers only.

Does the FDA agree with VIVUS' more focused, customized risk messaging approach to Qnexa prescribers post-launch?

Discussion: FDA agreed to remove the requirement for risk messaging at the 6-month timeframe; however, FDA disagreed with Vivus's plan (b) (4)

(b) (4)

- The FDA has proposed a dedicated Patient Coordination Center with a Call Center to handle stakeholders' REMS inquiries while VIVUS proposed using its Medical Information service center to process such inquiries. VIVUS is concerned that introducing additional contact numbers may cause undue confusion among stakeholders when existing resources, using REMS-experienced vendors, supported by training, standard procedures and FAQ scripts, will be sufficient to triage and address all REMS and product-related queries.

Discussion: FDA agreed that as long as there is sufficient coverage and staffing to address REMS-related questions, it is acceptable to have the same umbrella contact number but with separate triaging for REMS-related inquiries.

- The FDA has proposed that face-to-face, field-based access to REMS training be driven by medical liaisons. However, VIVUS would like to propose that all field-based personnel be able to offer (b) (4) for provider participation to improve the timeliness and reach of training activities, especially outreach to not-yet-trained prescribers. It would still be required that the provider review and answer the post-training assessment questions and enter their DEA# as verification of completion of training.

Does the FDA agree that training, in this (b) (4) format, can be offered by all VIVUS field-based personnel?

Discussion: FDA expressed concern regarding the quality of this proposed form of training. Concerns include that the training program takes 20 minutes, the "average" amount of face-to-face time a field representative gets with a HCP (according to Vivus) is 5-10 minutes, and the sales staff has competing priorities that could interfere with delivery of the training and risk message. Vivus will consider FDA concerns in this area and include another proposal for face-to-face training. The proposal will be included in the REMS submission March 30.

- The (b) (4) could be provided as part of the HCP training materials, but VIVUS proposes the possibility of either (1) a non-modifiable, teratogenicity and pregnancy prevention focused tool for WOCBP instead (b) (4) Either could be made available on the REMS website as a resource and providers or their support staff can choose to integrate into their counseling practices. VIVUS is concerned that a (b) (4) would be challenging or impossible to assess for effectiveness, based on not knowing what modifications have been made at each practice and how that impacted effectiveness.

Would the FDA find either (1) a non-modifiable, teratogenicity and pregnancy prevention focused tool for WOCBP within the REMS or (b) (4) be an acceptable means to address this counseling need?

Discussion: FDA agreed that the first approach, a non-modifiable tool within the REMS, would be acceptable, and that the checklist could be merged with this non-modifiable tool.

5. VIVUS would like to clarify the content and intent of the Patient Brochure. Previously the FDA said that such a document might be duplicative, and might detract from patient use of the approved Medication Guide. If a second document is generated, it will need to go to all patients (as CBP status is not provided by HCPs to pharmacies) consistent provision with the Med Guide. If included, to maximize reinforcement of important messages (risk of oral clefts, adequate contraception, pregnancy testing prior to and while on treatment, and need to stop Qnexa if pregnant), VIVUS proposes a 1-page "Special info for WOCBP" document derived directly from approved Med Guide language, that can be delivered as a pdf with the Med Guide, included in the DHCP letters, and is downloadable from the Qnexa REMS website. Vivus will provide a draft copy once an FDA-commented version of the Med Guide is available.

- a. Could the FDA confirm that it now wants a Patient Brochure?

Discussion: FDA agreed that a Patient Brochure would be part of the approved Qnexa REMS. The patient brochure would be included with every prescription, along with the Medication Guide.

- b. Does the FDA find the described 1-page "Special info for WOCBP" Patient Brochure content and format acceptable?

Discussion: Vivus will submit the Patient Brochure, which should include a graphic of an oral cleft. They will also submit the results of their patient focus group as Vivus has proposed (b) (4)

FDA also commented that the pregnancy surveillance program would not be included as part of the REMS or as a post-marketing requirement (PMR). It will be a voluntary program managed by the sponsor. A prospective cohort study to obtain pregnancy exposure data and offspring risk information will be a PMR. FDA agreed to provide expected data collection elements for the Pregnancy Surveillance program (see attachment).

6. VIVUS would also like the opportunity to receive comments on the content of the Qnexa training curriculum so that a (b) (4) website can be developed for review and approval. A copy of the document originally submitted on 12 March, 2012, as part of our Type C Meeting Briefing Book is attached.

Can the FDA provide clarification and feedback on the training curriculum outline?

Discussion: FDA commented that the training curriculum is generally acceptable, but FDA would need to see the actual materials. Psychiatric risk may be included, but the focus should be on the teratogenic risk. The information regarding [REDACTED] (b) (4) [REDACTED] should be removed.

7. Vivus has reviewed the requested assessment metrics from pharmacy data and has the following comments:
- Specialty data is not collected by pharmacies, and thus cannot be reported.
 - Collection of duration of use, episodes of use per patient, length of break in use for patients with multiple episodes of use data is complicated by HIPAA and the use of multiple pharmacies. Per HIPAA, pharmacies can't share patient level data, and any data compiled at a central database would need to be de-identified, significantly limiting our ability to gather and report these data with any assurance of completeness.

Vivus proposes removing these metrics from the FDA-proposed list of metrics. Does the FDA accept the removal of these metrics that the Sponsor believes will not be feasible to collect?

Discussion: FDA agreed that the requirement to provide the assessment metrics does not need to be a component of pharmacy certification; however, these metrics will remain a requirement of the REMS assessment.

Vivus was asked to provide all REMS materials in Word versions. Mock-up galley proof versions of REMS materials showing design layout and graphics should be provided so that the FDA can review the layout and graphics as well as the content of the materials.

3.0 ATTACHMENTS AND HANDOUTS

REMS document sent by FDA on March 16, 2012
Timeline of REMS deliverables presented by Vivus on March 21, 2012
Pregnancy Exposure Data Elements sent to Vivus on March 23, 2012

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immediately following this page

Additional comments:

1. REMS website: The REMS Communication materials should be maintained on a dedicated stand-alone REMS website. Include a prominent link on the product website's homepage for REMS materials. Any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a single-click, prominent direct link off the main website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The REMS-related webpage(s) should not be a means to promote this drug or any other product. Only the separate webpage(s) and /or link will be considered a component of the REMS.
 - The landing page of the separate REMS link should contain brief background information on the REMS along with the REMS educational materials.
 - This page should include a prominent header to communicate the risks addressed through the REMS.
 - We recommend the following language as background information on the REMS landing page:

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks. [sponsor name] has worked with the FDA to develop materials to communicate the risks of [list risks] to healthcare providers.]

(b) (4)

3. We propose changing the Patient-Provider Agreement Template to a modifiable (by the end user) patient counseling tool. This piece should focus solely on the teratogenic risk associated with the use of Qnexa. The language in this counseling tool should be understandable by patients. Although prescribers may wish to obtain a patient signature for their own purposes, the Agency has no interest in obtaining such signatures. The activities under the communication plan should be included under ETASU A, (b) (4)
4. The implementation system should include details on how certified pharmacies will receive Qnexa. If you will not be shipping Qnexa directly to the certified pharmacies, how will you be sure that distributors are shipping Qnexa only to certified pharmacies?
5. The REMS does not explain how you will include large closed systems (e.g., Kaiser Permanente, the VA) in the REMS.
6. A comment was voiced at the advisory committee meeting that information about contraceptive use for patients receiving Qnexa should incorporate evidence regarding effective contraceptive use specific for these patients; i.e., obese patients taking Qnexa.

Table 2 that details acceptable contraception within the REMS should incorporate such considerations, to the extent possible.

7. Clarify what would constitute completed training via monographs or other print means. Delivery of such materials would not be sufficient to accomplish training without confirmation that the materials were read. We have included proposals to this end in the draft REMS
8. The REMS should include a timeframe for contacting prescribers and new prescribers for training, what the contact and follow-up contacts with the prescriber for training will entail.
9. Because it is expected that patient counseling will be undertaken by persons other than the prescriber, the training should include information and materials for use by allied health providers and office staff. The training should be offered to these additional HCPs. This should include a checklist/algorithm for use by the prescriber or support staff, and a patient brochure to be given to the patient as a reminder, listing what the patient should do in preparation for taking Qnexa, and while taking Qnexa. This should include possible GYN consult, information about oral clefts, pregnancy testing prior to beginning Qnexa, contraceptive advice, monthly pregnancy testing, and stopping rules. To help the patient understand oral clefts, an image of an oral cleft should be included.
10. Your assessments should include, but not be limited to the following:
 - a. From surveys of patients
 - a. Evaluation of patients' understanding of the serious risks of Qnexa
 - b. Evaluation of extent that WOCBP were counselled about pregnancy prevention & contraceptive use
 - c. Evaluation of contraceptive use by WOCBP
 - b. From surveys of HCPs,
 - a. Evaluation of healthcare provider's understanding of the serious risks of Qnexa
 - b. An assessment of healthcare provider's awareness of:
 - i. The need to exclude a pregnancy before initiating Qnexa therapy
 - ii. The need for patients to use adequate birth control and what the accepted forms of contraception are
 - iii. The need to promptly discontinue Qnexa therapy in the event of a pregnancy.
 - c. Evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed
 - d. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - e. With regard to the DHCP letter: The date of initial mailing of the DHCP letter to HCPs and professional organizations and subsequent mailings, the number of recipients of the DHCP letter, a copy of all documents included in each distribution

- f. Data establishing the date, number and specialty of health care providers (HCPs) targeted via email, the number and specialty of HCPs who received the email, and number and specialty who opened the email, number of emails that were undeliverable, the number of letters send hard copy and distributed by sales representatives, the names of professional organizations contacted to distribute the DHCP letter to their members, the names of the organizations who accepted and redistributed the letter, and the names of the professional organizations who declined to accept or redistribute the DHCP letter.
- g. An assessment of the percentage of targeted physicians who are presented with REMS materials via Sales Specialists, the website, or medical information department
- h. An assessment of the number and percentage of unique prescribers who undergo the educational training (during the reporting period and cumulative), and the number of other non-prescriber HCPs who complete the training.as defined within the REMS
 - a. For electronic training, viewing of all module training screens or pages and completion of post-training assessment questions
 - b. For print training modules delivered in person by medical liaison, a statement by the medical liaison that the training module was completed
 - c. For print training modules completed independently by the HCP, mailing or faxing a tear-off statement of completion of the training
- i. An assessment of strategies that have been employed to encourage prescribers to undergo educational training
- j. The number of certified pharmacies under agreement with Vivus for this program
- k. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance, including information regarding Qnexa dispensed outside of certified pharmacies (amount, # instances)
- l. The number of pharmacies decertified and the reason for the decertification; pharmacies will be decertified for failing to enact the elements of the REMS required for pharmacy certification [Vivus: put in the REMS supporting document how you will handle each infraction, and the point at which pharmacies would be decertified.]
- m. data on patients receiving Qnexa including dosage strength prescribed, the age and sex of patients receiving Qnexa, duration of use, episodes of use per patient, length of break in use for patients with multiple episodes of us
- n. data on prescribers of Qnexa including the number of unique prescribers prescribing Qnexa, by specialty (during the reporting period and cumulative)
- o. Information on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii)

and including any material or significant updates to the status information since the annual report was prepared.

REMS Deliverable	Provided by VIVUS to FDA	Comments by FDA back to VIVUS
Label	Emailed to FDA March 21 st	
Medication Guide		Awaiting FDA comments
Updated Proposed REMS Document	March 30 th	
Updated REMS Supporting Document (REMS SD)	March 30 th	
Dear HCP Letter (REMS SD)	March 30 th	
Dear Pharmacist Letter (REMS SD)	March 30th	
Dear Medical Society Letter (REMS SD)	March 30th	
Targeted Prescriber Follow-on Communication Plan for 6, 12, 24 months (REMS SD)	March 30 th	
REMS Website Landing page (REMS SD)	March 30 th	
	(b) (4)	
1-pg Pregnancy prevention focused provider counseling tool (previously PPA; REMS SD)	March 30 th	
1-pg Important Information for WOCBP (previously the Patient Brochure; REMS SD)	March 30 th	
Final version of Provider Training Curriculum (REMS SD)		Awaiting FDA Comments
REMS assessment Plan (REMS SD)	March 30 th	
Patient Selection and Initiation Checklist (REMS SD) and Patient Management Algorithm (REMS SD)	March 30 th	
Confirmation of database fields for Pregnancy Surveillance database – outside REMS		Awaiting FDA Comments

All listed documentation will be provided to the FDA by VIVUS on March 30th.
We would like to request a follow-up meeting on or before April 9th to finalize.

Data Elements to Consider Collecting for Pregnancy Exposure

A. General

Patient identifier

Name of reporter at initial contact

Date of initial contact

Dates of any follow-up contacts

Telephone number of reporter

Additional contact names and phone numbers (if reporter is the patient)

B. Maternal Information

Source of information (e.g., obstetrician, pregnant woman, other)

Birth date

Race

Occupation

Maternal medical history (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, allergic disorders, heart disease, connective disease, autoimmune disease, hepatitis, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures, other)

Obstetrical History:

Number of pregnancies and outcome of each (live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy)

Previous maternal pregnancy complications

Previous fetal/neonatal abnormalities and type

Current Pregnancy:

Date of last menstrual period

Complications during pregnancy (including any adverse drug reactions) and dates

Number of fetuses

Labor/delivery complications

Disease course(s) during pregnancy and any complications

Medical product exposures (prescription drugs, OTC products & dietary supplements):

Name

Dosage & route

Date of first use & duration

Indication

Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount

Family History (specify type, maternal/paternal, etc.):

Spontaneous Abortions

Anomalies/Malformations

Multiple fetuses/births

C. Neonatal Information

Initial:

Source of information (e.g., obstetrician, pediatrician, mother)

Date of receipt of information

Date of birth or termination

Gestational age at birth or termination

Gestational outcome (live born, fetal death/stillborn, spontaneous abortion, elective termination)

Sex

Pregnancy weight gain of mother

Obstetric complications (e.g., pre-eclampsia, premature labor, premature delivery)

Pregnancy order (singleton, twin, triplet)

Results of neonatal physical examination including

 Anomalies diagnosed at birth or termination

 Anomalies diagnosed after birth

 Weight at birth indicating whether small, appropriate, or large for gestational age

 Length at birth

 Condition at birth (including when available Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)

Neonatal illnesses, hospitalizations, drug therapies

Follow-up:

 Source of information (e.g., pediatrician, mother)

 Date of receipt of information

 Anomalies diagnosed since initial report

 Developmental assessment

 Infant illnesses, hospitalizations, drug therapies

Note: Infants should be followed for 12 months with assessment times at birth, at 12 months, and some point in between.

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/s/

POOJA DHARIA
03/27/2012

From: [Dharia, Pooja](#)
To: ["Malcolm McKay"](#)
Subject: Qnexa information request 3/8/12
Date: Thursday, March 08, 2012 3:24:00 PM

Hi Malcolm,

Please see below for information requests for Qnexa:

1. Your requests for a deferral in 12 to 17 year olds and a waiver in 0 to (b) (4) year olds have been reviewed by the Division and the Pediatric Review Committee (PeRC).

At this time we are granting a deferral in 12 to 17 year olds and agree to a waiver in 0 to 6 year olds. The Division and PeRC agreed to (b) (4) grant a deferral for the 7 to 11 year old age group.

In addition, it is strongly encouraged that a future Proposed Pediatric Study Request evaluate the safety and effectiveness of QNEXA in children/adolescents affected by genetic/syndromic causes of obesity such as Prader Willi.

2. Please submit a debarment certification and financial disclosure certification. If nothing has changed since your original submission, you will need to submit a letter referencing the original certifications.

Thanks,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

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/s/

POOJA DHARIA
03/08/2012

From: [Suggs, Courtney](#)
To: [Dharia, Pooja](#)
Cc: [Parks, Mary H](#); [Mathis, Lisa](#); [Addy, Rosemary](#); [Greeley, George](#)
Subject: NDA 22-580 Qnexa (phentermine/topiramate)
Date: Thursday, March 08, 2012 4:03:45 PM
Attachments: [1 Pediatric Record.pdf](#)

Hi Pooja,

The email serves as confirmation of the review for the Qnexa (phentermine/topiramate) product conducted by the PeRC PREA Subcommittee on March 7, 2012.

The Division presented a partial waiver for patients ages 0 to 6 years of age because the product fails to represent a meaningful therapeutic benefit and is unlikely to be used in a substantial number of patients and a deferral for those 7 to (b)(4) years of age because adult studies are ready for approval for the treatment of obesity, including weight loss and maintenance of weight loss, in conjunction with diet and exercise.

The PeRC agreed with the Division to grant a partial waiver for patients 0 to 6 years of age and a deferral in patients 7 to (b)(4) years of age.

The PeRC offers the following recommendations:

- PeRC recommends incorporating ophthalmic exams, bone mineral density testing, and monitoring for neurocognitive adverse effects in deferred pediatric studies.
- The PeRC recommends studying other pediatric obesity indications if the Division issues a future WR.
 - PeRC members would be willing to assist the Division if needed in selecting the obesity indications (including syndromic obesity indications) to include; however, the Division could request that the Sponsor include all potential indications in a PPSR.
- The PeRC recommends the Division include more details about what they want in a juvenile animal study PMR.
- The PeRC recommends the Division change the reason for waiving pediatric studies to the product would be ineffective and/or unsafe in one or more of the pediatric groups to give the Division a mechanism to incorporate pediatric safety information from topiramate labeling into Qnexa labeling.
- The PeRC agrees with and likes the staggered approach for conducting deferred studies in pediatric patients.

The pediatric record is attached for Qnexa.

Thanks,

Courtney M. Suggs, Pharm.D., MPH

LCDR, USPHS

Regulatory Project Manager

Pediatric and Maternal Health Staff

Office of New Drugs, Immediate Office

Center for Drug Evaluation and Research

US Food and Drug Administration

10903 New Hampshire Ave.

Bldg 22, Room 6471

Silver Spring, MD 20993

Phone: (301) 796-2096

Email: courtney.suggs@fda.hhs.gov

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/s/

POOJA DHARIA
03/14/2012



NDA 022580

MEETING MINUTES

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for QNEXA (phentermine/topiramate) Extended Release Capsule.

We also refer to the meeting between representatives of your firm and the FDA on January 12, 2012. The purpose of the meeting was to continue to discuss the REMS that Vivus submitted with the QNEXA Complete Response submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: Thursday January 12, 2012, 2:00 – 3:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: NDA 022580
Product Name: QNEXA (phentermine/topiramate)
Extended Release Capsule
Indication: Obesity
Sponsor/Applicant Name: Vivus, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy G. Egan, M.D., M.P.H.	Deputy Director for Safety
Mary Roberts, M.D.	Clinical Reviewer
Julie Marchick, M.P.H.	Chief, Project Management Staff
Pooja Dharia, Pharm.D.	Regulatory Project Manager

Office of Surveillance and Epidemiology

Jing (Julia) Ju, Pharm.D., Ph.D.	Pharmacoepidemiologist, Division of Epidemiology (DEPI)
Diane Wysowski, Ph.D.	DEPI Team Leader
Joyce Weaver, Pharm.D.	Senior Risk Management Analyst, DRISK
Cynthia LaCivita, Pharm.D.	Director, DRISK
Claudia Karwoski, Pharm.D.	Risk Management Analyst Team Leader, DRISK

NDA 022580
Meeting Minutes
January 12, 2012

Pediatric and Maternal Health Staff

Jeanine Best, MSN, RN, PNP	Senior Clinical Analyst
Melissa Tassinari, Ph.D., DABT	Acting Team Leader, PMHS - Maternal Health

SPONSOR ATTENDEES

Wesley Day, Ph.D.	V.P. Clinical Development
Malcolm McKay, Ph.D.	V.P. Regulatory Affairs and Corporate Compliance
Michael P. Miller, M.B.A.	SVP, Chief Commercial Officer
Craig Peterson, M.S.	Senior Director, Clinical Development

(b) (6)

Peter Tam, M.B.A.	President
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(b) (6)

Barbara Troupin, M.D., M.B.A.	Sr. Director Medical Affairs
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1.0 BACKGROUND

Qnexa (PHEN/TPM) is a combination of two marketed products, phentermine and topiramate, indicated for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). The proposed doses for marketing are three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg.

A Complete Response letter was issued on October 28, 2010. Vivus submitted the complete response to this letter on October 17, 2011.

The purpose of this meeting is to review the questions Vivus has proposed in the briefing document and to discuss any additional comments regarding the Risk Evaluation and Mitigation Strategies (REMS) that Vivus submitted with the QNEXA Complete Response Submission.

2.0 DISCUSSION

Your questions are repeated below, followed by our response in **bold** print, with discussion in *italics*:

1. Does FDA agree that the revised indication and contraindication for Qnexa are consistent with regulatory definitions?

FDA Response: If the drug is approved, the indication will be discussed as part of labeling negotiations.

Since the contraindication is integral to your proposed risk mitigation proposal, we can provide the following comments. (b) (4)
Your product will need to be contraindicated in pregnant women. The contraindication will also need to note that if a woman becomes pregnant while taking Qnexa that Qnexa should be discontinued immediately.

We would like your perspective on why you feel (b) (4) **is necessary.**

Discussion: FDA responded that the proposed pregnancy contraindication complies with the current pregnancy labeling regulations, and also incorporates the “spirit” of the proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The pregnancy subsection of labeling should provide information only on the use of a drug during pregnancy. Information for non-pregnant females of reproductive potential should be placed elsewhere in labeling. These issues will be discussed during labeling negotiations and will not be discussed during the advisory committee.

2. Does FDA agree that the teratogenic risk associated with Qnexa can be managed through labeling and a REMS composed primarily of educational measures?

FDA Response: If Qnexa is approved, we believe that the teratogenic risk associated with Qnexa might be adequately mitigated through a combination of physician and patient labeling and a REMS. The elements of the REMS we consider appropriate at this time are a Medication Guide to inform patients regarding the teratogenic risk associated with Qnexa, a Communication Plan to inform prescribers about the teratogenic risk associated with Qnexa and to support implementation of the REMS, an ETASU consisting of healthcare provider training and pharmacy certification, and a timetable for submission of assessments of the REMS. We considered a REMS with restrictive elements, but believe it may drive prescribers to use the currently approved individual ingredients for weight loss.

It is not necessary that all of the communication and training materials be ready in advance of the Advisory Committee as we do not, at this time, anticipate discussing such details of your proposed REMS.

Discussion: The sponsor proposed to discuss the different elements of the REMS and the pros/cons of each at the Advisory Committee, as it is necessary to show the panel how the REMS will mitigate the risk. The sponsor's discussions with stakeholders revealed that they are primarily worried about [REDACTED] (b) (4). The sponsor proposed [REDACTED] (b) (4)

Post-meeting note: [REDACTED] (b) (4)

3. Does FDA have any other comments regarding labeling at this time?

FDA Response: No. At this time it is premature to discuss labeling.

Discussion: No discussion occurred.

4. Does FDA agree with the revised REMS goals for Qnexa?

FDA Response: We propose the following REMS goals:

- **To inform prescribers and females of child-bearing potential about:**
 - **the risk of congenital malformation associated with fetal exposure to Qnexa during pregnancy**
 - **the importance of pregnancy prevention**
 - **the need to minimize fetal exposure**

Discussion: FDA confirmed that [REDACTED] (b) (4) was removed as one of the goals of the REMS.

5. Does FDA agree that the revised proposed REMS is sufficient to address the risk of teratogenicity for Qnexa, while not being overly burdensome?

FDA Response: We find the REMS we have proposed under question 2 to be sufficient. We have concerns regarding the number of materials and the frequency of the dissemination of those materials that you have proposed. We feel it may contribute to “information fatigue”. However, we will continue to advise you on the appropriateness of your proposed materials and the frequency of their distribution after we have seen and reviewed them.

Discussion: No discussion occurred.

6. Does FDA agree that the enhanced educational measures are properly categorized as a “safe use conditions” ETASU?

FDA Response: The REMS ETASU that is being proposed for your product is an ETASU A: “HCP’s who prescribe the drug have particular training or experience, or are specially certified”, and ETASU B: “Pharmacies, practitioners, or health care settings that dispense the drug are specially certified”.

Discussion: FDA noted that, while HCP training is “voluntary”, Vivus would be expected to ensure that prescribers undergo the training.

7. Does FDA agree with the proposed REMS assessments and frequency?

Response: We will continue to work with you regarding your surveys and survey methodology. The REMS assessments should be conducted at 6 months, 12 months and then annually from the initial approval of the REMS. This is Agency standard for ETASU REMS.

Discussion: No discussion occurred.

8. Is FDA in agreement that the voluntary measures add to the risk mitigation plan for Qnexa?

FDA Response: As you can see from our response to question 2, we are proposing to make the specialty pharmacy part of the ETASU.

We have concerns about the volume of materials that you propose. We also have concerns regarding redundancy in the messaging, e.g., what does the Patient Brochure provide that the Medication Guide does not? Will it detract from patients reading the Medication Guide?

We have no further comment on your other voluntary measures.

We have not reached final agreement on what studies we would require post-marketing. If the drug is approved, we would be interested in determining outcomes from fetal exposure to Qnexa, as well as determining why the educational/informational materials may not be effective in keeping pregnant women from taking Qnexa. To that

end, we are considering a study similar in design to FORTRESS, but for Qnexa. Such a study would help us gather information on the frequency of pregnancies that are occurring and any malformations associated with Qnexa use. It would also provide us with data as to whether patients are taking Qnexa or the individual components, as well as information on dosing and duration of therapy.

We are also considering having you explore the use of the Organization of Teratology Information Specialists (OTIS) database for pregnancies occurring in patients receiving Qnexa, and the outcomes of those pregnancies.

Finally, we are considering having you, as part of your REMS assessment, survey females of child-bearing potential who stop taking Qnexa. We would like to know why they stopped taking drug, specifically if it was because they became pregnant. Those surveys would try to get at the root cause for the fetal exposure.

Discussion: FDA indicated it would provide Vivus with an article from the published medical literature describing the OTIS database.

9. Does FDA have any suggestions on the recommended voluntary measures?

FDA Response: Please see response to question 8 above.

Discussion: No discussion occurred.

10. What question or questions does FDA intend to pose to EMDAC regarding the Qnexa REMS?

FDA Response: At this time we do not anticipate that there will be a specific question regarding the REMS, rather the REMS will be a consideration in the overall benefit-risk assessment. A question such as “Given the proposed REMS, do the benefits of Qnexa outweigh the risks?” would be the kind of general question that might be asked.

The Agency’s presentation will outline why FDA thinks that the REMS we have outlined in question 2 might be appropriate for this product.

Discussion: Vivus proposed modifying any such question to allow some flexibility in the type of REMS the Advisory Committee might find useful, e.g. “With an appropriate REMS, do the benefits of QNEXA outweigh the risks?” FDA acknowledged Vivus’ comment and indicated that the questions for the Advisory Committee are still undergoing internal discussion.

11. In the event the EMDAC finds the Qnexa REMS inadequate, will FDA seek EMDAC feedback on the adequacy and feasibility of a contraindication in WOCBP?

FDA Response: At this time, we do not intend to ask the committee specific questions about the adequacy of the REMS, nor do we intend to discuss labeling at the Advisory Committee meeting.

Discussion: No discussion occurred.

Additional Comment:

12. **While we think it would be helpful for the Advisory Committee members to have a general understanding of the tools you intend to employ in your REMS, we are not seeking an in-depth presentation of your proposed materials. We do think that you should provide general comments to the Advisory Committee staff as to what you will be looking for in your REMS assessments, i.e., what important information you could glean from your assessments that will allow you to understand why patients fail despite the REMS, and how that would inform future modifications to the REMS.**

Discussion: No discussion occurred.

3.0 ATTACHMENTS AND HANDOUTS

Slides presented by Vivus on January 12, 2012

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/s/

POOJA DHARIA
01/30/2012



NDA 022580

MEETING MINUTES

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for QNEXA (phentermine/topiramate) Extended Release Capsule.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2011. The purpose of the meeting was to discuss the REMS that Vivus submitted with the QNEXA Complete Response submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: Monday December 19, 2011, 11:00 – 12:30 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: NDA 022580
Product Name: QNEXA (phentermine/topiramate)
Extended Release Capsule
Indication: Obesity
Sponsor/Applicant Name: Vivus, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy Egan, M.D.	Deputy Director for Safety
Mary Roberts, M.D.	Clinical Reviewer
David Carlson, Ph.D.	Pharmacology Toxicology Reviewer
Julie Marchick	Chief, Project Management Staff
Pooja Dharia, Pharm.D.	Regulatory Project Manager
John Bishai, Ph.D.	Safety Regulatory Project Manager

Office of Surveillance and Epidemiology

Jing (Julia) Ju, Pharm.D., Ph.D.	Pharmacoepidemiologist, Division of Epidemiology (DEPI)
Joyce Weaver, Pharm.D.	Senior Risk Management Analyst, DRISK
Cynthia LaCivita, Pharm.D.	Director, DRISK
Claudia Karwoski, Pharm.D.	Risk Management Analyst Team Leader, DRISK
Ermias Zerislassie	
Christian Hampp	

Pediatric and Maternal Health Staff

Jeanine Best, MSN, RN, PNP	Senior Clinical Analyst
Melissa Tassinari, PhD, DABT	Acting Team Leader, PMHS - Maternal Health

SPONSOR ATTENDEES

Wesley Day, Ph.D.	V.P. Clinical Development
Malcolm McKay, Ph.D.	V.P. Regulatory Affairs and Corporate Compliance
Michael P. Miller, M.B.A.	SVP, Chief Commercial Officer
Craig Peterson, M.S.	Senior Director, Clinical Development

[Redacted] (b) (6)

Peter Tam, M.B.A.	President
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[Redacted] (b) (6)

Barbara Troupin, M.D., M.B.A.	Sr. Director Medical Affairs
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1.0 BACKGROUND

Qnexa (PHEN/TPM) is a combination of two marketed products, phentermine and topiramate, indicated for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). The proposed doses for marketing are three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg.

A Complete Response letter was issued on October 28, 2010. Vivus submitted the complete response to this letter on October 17, 2011.

The purpose of this meeting is to review the questions Vivus has proposed in the briefing document and to discuss any additional comments regarding the Risk Evaluation and Mitigation Strategies (REMS) that Vivus submitted with the QNEXA Complete Response Submission

2.0 DISCUSSION

Your questions are repeated below, followed by our response in **bold print**, with discussion in *italics*:

1. The Sponsor proposes a QNEXA REMS program addressing

(b) (6)

(b) (6)

Does the Division agree that the Sponsor's goals for the QNEXA REMS adequately address the major risks of concern for QNEXA?

FDA Response: No.

(b) (6)

(b) (6)

Response sent by Vivus on 12/18/11: Regarding the Division's preliminary response to Question 1, VIVUS would like to clarify whether the approvability of Qnexa is contingent on a REMS with goals and elements that would manage off-label use of topiramate?

Discussion: FDA clarified that the currently proposed REMS does not take into account that the individual component drugs are available on the market. The REMS should not be so overly burdensome that it diverts patients to the individual components. The major risks that FDA is concerned about are teratogenicity and suicidality. The focus of the REMS should be education of patients and providers. FDA acknowledges that no REMS can prevent potential fetal exposure to QNEXA in all cases, but would like the sponsor to analyze reasons why the strategies proposed may not meet their intended goal in the post-marketing setting, and suggest approaches to improve education and compliance.. However, FDA does not expect that the REMS should have to mitigate the risk of off-label use of topiramate. The final REMS will take into account discussion at the February 22, 2012 Advisory Committee.

Vivus shared their proposals for the REMS. Please refer to attachment.

2. Does the Division agree that the proposed REMS and restricted distribution system will adequately mitigate the teratogenic risk of topiramate?

FDA Response: No.

(b) (6)

(b) (6)

We agree that patient and prescriber education about the serious risks of QNEXA should be the focus of any risk mitigation strategy. We suggest you look at a spectrum of options, but focus on less highly restrictive measures than what you have proposed. You should weigh the pros and cons of each approach before you settle on a final strategy. You should not assume that a more restrictive REMS improves the likelihood of approvability of your product. Please also keep in mind when looking at REMS options how the success of your REMS program can be adequately assessed.

Response sent by Vivus on 12/18/11: Does FDA believe that a robust Medication Guide and Communication Plan may be sufficient to manage the risk of Qnexa in women of childbearing potential?

Discussion: FDA noted that Communication Plans are limited in their duration, but that an educational program under an ETASU would allow for an ongoing program. So, a MG and CP-only REMS would not likely be sufficient. FDA noted that the pregnancy

registry is still under internal discussion. However, (b) (4) will be overly burdensome and expensive. FDA reiterated that the REMS should not be so overly burdensome that it diverts patients to the individual components

Vivus discussed the proposed (b) (6)

(b) (6)

3. Does the Division agree with the proposed content and frequency of REMS assessments?

FDA Response: The proposed timetable of assessments will be considered during the review process. Additional assessment points will be required, beyond knowledge and understanding, and will be communicated during the review process.

Discussion: No discussion occurred.

4. The proposed QNEXA REMS design maximally leverages existing pharmacy data management systems to (b) (6) based on demographic and exception documentation. The proposed REMS is intended to avoid undue administrative burdens and non-compliance vulnerabilities.

Question 4A: Does the Division foresee deficiencies with this approach?

FDA Response: We do not agree (b) (6)

We defer comment at this time on your proposal to leverage existing pharmacy systems.

Discussion: No discussion occurred.

Question 4B: Does the Division have any recommendations to strengthen the proposal's design?

FDA Response: See responses to questions 1 and 2 above. We invite your ideas on how to create a robust program that engages stakeholders and promotes safe use without linking participation in the program to drug access.

Discussion: No discussion occurred.

5. Use of QNEXA is [REDACTED] (b) (6) [REDACTED] (b) (6)

- a. Does the Division agree that the QNEXA [REDACTED] (b) (6) is appropriate [REDACTED] (b) (6)

FDA Response: No, [REDACTED] (b) (6)

Discussion: No discussion occurred.

- b. Does the Division believe that there are additional sub-populations (e.g., BMI > 35 with a weight-related co-morbidity or BMI > 30 with two co-morbidities) for whom the risk benefit profile may be favorable given the current understanding of the teratogenic risk of topiramate? If so, could the Division please elaborate?

FDA Response: At this time, we do not believe it would be feasible or justified to limit use of QNEXA to [REDACTED] (b) (4) with, for example, a BMI > 35 kg/m² with a weight-related comorbidity.

Discussion: No discussion occurred.

6. Does the Division agree that VIVUS has adequately addressed the heart rate concern identified within the CRL? Is the proposed label adequate to manage the potential increased HR risk?

FDA Response: We continue to discuss the heart rate data and their potential implications regarding approval of QNEXA. We encourage you to submit a protocol for the planned cardiovascular outcome study and strongly recommend that you discuss this proposed trial at the February 22, 2012, advisory committee meeting. It is premature to discuss labeling prior to the advisory committee meeting and the final review of the complete response.

Discussion: Vivus will be submitting a draft CV protocol in the next few weeks. The study will be a 5-6 year study enrolling 15,000 patients globally and will be a superiority trial, using MACE as an endpoint. The background rate of MACE is targeted at 1.5 to 1.75%. The sponsor is discussing the percentage of individuals in North America that will be enrolled in this study. The Division encouraged the sponsor to enroll at least 25-50% from North America.

7. Does the Division intend to revisit cognitive effects, neuropsychiatric effects and metabolic acidosis at the upcoming Advisory Committee? Aside from the issues addressed in our Complete Response Letter (CRL), are there additional issues the Division plans to raise during the upcoming QNEXA Advisory Committee?

FDA Response: The agenda has not been finalized for the advisory committee meeting. However, a summarization of QNEXA's safety profile will be discussed.

Discussion: Vivus proposed to discuss four main topics: 1) Summary of safety, including two-year data; 2) REMS proposal; 3) CV outcomes study, including CV safety; and 4) teratogenicity, including data from SLOAN, CDC and top-line results from FORTRESS.

8. Does the Division agree with VIVUS' proposed recommendations in the Dosing and Administration section of the draft label (Cross Reference NDA 22,580; Serial Number 0056, Module 1.14.1.2 Annotated Draft Labeling, Dosage and Administration).

FDA Response: It is premature to discuss labeling prior to the advisory committee meeting and the final review of the complete response.

Discussion: The sponsor acknowledged they do not have data supporting the proposed recommendations in the Dosing and Administration section.

3.0 ATTACHMENTS AND HANDOUTS

Handout sent by Vivus on December 18, 2011

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/s/

POOJA DHARIA
01/10/2012



NDA 022580

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

We acknowledge receipt on October 17, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for QNEXA (phentermine/topiramate) Extended Release Capsule.

We consider this a complete, class 2 response to our October 28, 2010, action letter. Therefore, the user fee goal date is **April 17, 2011**.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

POOJA DHARIA
11/01/2011

MEMORANDUM OF TELECON

DATE: September 7, 2011

APPLICATION NUMBER: NDA 022580

DRUG NAME: Qnexa (phentermine/topiramate) capsule

BETWEEN:

Vivus, Inc.

Peter Tam, MBA – President

Wesley W. Day, Ph.D. – V.P., Clinical Development

Craig Peterson, M.S. – Sr. Director, Clinical Development

AND:

Division of Metabolism and Endocrinology Products

Eric Colman, M.D. – Deputy Director

Mary Roberts, M.D. – Clinical Reviewer

Pooja Dharia, Pharm.D. – Regulatory Project Manager

Patricia Madara – Regulatory Project Manager

BACKGROUND

Qnexa (PHEN/TPM) is a combination of two marketed products, phentermine and topiramate, indicated for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). It will be available in three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg.

A Complete Response letter was issued on October 28, 2010. An End of Review Conference was held on January 19, 2011 and follow-up meeting was held on April 14, 2011, during which an in-depth retrospective observational study of congenital malformations and birth weight in fetuses of women treated with topiramate for migraine prophylaxis was requested by FDA.

Vivus submitted the protocol for the observational study entitled, *OB-901 (FORTRESS): Fetal Outcome Retrospective study of TopiRamate ExpoSure Study* on May 27, 2011 and received FDA feedback on July 19, 2011.

TELECONFERENCE

A teleconference was held to discuss FDA's current view on recently revealed teratogenicity data, i.e. SLOAN/CDC data. FDA responded that this data would be evaluated with the NDA resubmission and after discussion with OSE.

Vivus confirmed that the NDA would be resubmitted with the limited indication use in mid to late-October 2011. The resubmission would include a manuscript submitted to the International Epilepsy Congress entitled, *Retrospective analysis of major congenital malformations (MCMs) and oral clefts (OC) associated with in utero topiramate exposure.*

FDA indicated that the Advisory Committee for Qnexa would likely occur during late January or early February 2012. The scope of the meeting would focus on issues outlined in the Complete Response letter, including, but not limited to, teratogenicity, cardiovascular risk and 2-year efficacy data. Vivus indicated that there would be extensive REMS discussion before the Advisory Committee occurred.

Memo prepared by: Pooja Dharia, Pharm.D. - Regulatory Project Manager
Concurrence by: Eric Colman, M.D. – Deputy Director

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/s/

POOJA DHARIA
09/08/2011



NDA 022580

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your new drug application (NDA) dated and received December 28, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for QNEXA (phentermine/topiramate) Extended Release Capsule.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JULIE C MARCHICK

09/01/2011

J. Marchick signing for M. Parks



IND 068651
NDA 022580

GENERAL ADVICE

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for QNEXA (phentermine/topiramate) Extended Release Capsule.

We also refer to your May 27, 2011, submission, containing the protocol for OB-901 entitled, *FORTRESS: Fetal Outcome Retrospective study of TopiRamate ExpoSure Study*.

We have the following comments and recommendations. Your questions are repeated below, followed by our response in **bold** print.

1. Does FDA agree with the two control cohorts defined in the study protocol?

FDA Response: Yes. The choice to have two separate control cohorts in order to control for the effects of both prior TPM/AED exposure and indication is acceptable. While taking multiple matching pairs can lead to some increase in power, it is important to note that the exposed dyads are essential in the analysis and every attempt should be made to avoid discarding any exposed dyad. Thus, if some mother/infant exposed dyads do not have 7 available matched control pairs, it is recommended that the number of matched pairs for each exposed dyad be reduced within reason, rather than eliminating any exposed pairs from the study. You should finalize the list of diagnosis and procedure codes to assemble the study cohorts and identify relevant exposures, outcomes, and covariates for further evaluation.

2. Does FDA agree with our definition of TPM –exposed dyads for inclusion in the analysis?

FDA Response: Yes.

3. Does FDA agree with the analysis plan as outlined in the protocol?

FDA Response: More details on the analytical methods for each analysis and the approaches to combine results across data sources should be provided to FDA. Please submit a finalized Analytic and Reporting Plan for further comments.

4. Does FDA agree that we could resubmit the Qnexa NDA based on the results of automated data analysis with the validation work to be submitted during the 6- month review period?

FDA Response: In terms of this proposed observational study alone, you should be aware that data from a claims-only analysis would be considered preliminary data, unless compelling data suggesting that the outcome codes had already been validated in the same or relevant data sources are provided. A complete and final study protocol should be submitted to the FDA for review to determine if it is acceptable for initiating the study.

5. Are there any other major issues that need to be addressed?

FDA Response: Please see additional comments. The recommendations and points should be addressed in a revised protocol and statistical analysis plan.

Additional Comments:

6. You should provide the list of states that are included in the Thomson Reuters MarketScan Multi-State Medicaid Research Database and explore the possibility to include additional Medicaid data in the study.
7. You should describe and justify a method on how history of infection with TORCH agents and history of alcohol abuse or substance abuse will be identified and confirmed using claims data.
8. You should provide a description of how data from the multiple databases will be combined and if any attempts will be made to adjust for each database in the analysis.
9. When identifying dyads as cases for the endpoint of interest the following should be considered:
 - a. You should identify the cases of MCMs within 30 days of the delivery date on the mother's claims or within 365 days, instead of 90 days, of birth date on the infant's claims.
 - b. Ideally, you should validate all potential cases of MCMs identified from the automated data. If you choose to validate a subset of potential cases, you should justify your selection of the subset. The subset of cases to be validated should be chosen scientifically from the potential cases identified in the study cohorts and the PPV should be estimated using both the base case definition and the secondary, more restrictive case definition.
10. The sample size calculations provided in the protocol appear to have changed based upon your June 15, 2011, communication in which you state that the HealthCore Integrated

Research Database has been withdrawn from the list of databases you planned to utilize in your study. Absent the HealthCore database, we have concern about the power of the study to rule out a clinically meaningful level of risk. With the withdrawal of the HealthCore Integrated Research Database from the originally proposed sources, it may become possible to use other databases that contain overlapping data with HealthCore. Also, in your sample calculation you should provide a clear assumption of the relative risk along with appropriate terminology to define the objective being assessed (e.g. ruling out a given relative risk rate under non-inferiority or detecting a minimum increase with a certain amount of power). As we are not able to reproduce your sample size calculations at this time and with concerns about the power of the study, we recommend that the above issues be addressed in a revised protocol.

11. The following should be considered in revising your statistical methods for the primary analysis:
 - a. You should assess the prevalence and prevalence ratio of MCMs including OCs in analyses for both the primary and secondary study objectives.
 - b. The “stratified analysis” specified in the protocol would not allow for easily interpretable inference of the results. With such a small number of events anticipated for OCs, it will be common for the apparent relative risk in a stratum to shift based on a difference of very few events from one strata to another. Also, it will have little power to detect true signals. This analysis will likely be difficult to interpret.
 - c. A propensity score analysis may be a useful statistical analysis method for the small number of events anticipated in OCs. Propensity scores could be calculated by modeling the risk of TPM exposure during the first trimester based on covariates of possible influence (such as maternal age, indication, etc.). These propensity scores can then be used to match subjects from the Exposure Cohort to the two Control Cohorts, and then an analysis method such as McNemar’s test can be used on these pairs to attempt to discern a difference in event rates between the cohorts.
 - d. Multivariate logistic regression on the occurrence of MCMs would seem to be an acceptable method for the analysis of the MCM endpoint. Covariates for this model should be pre-specified based on a clinical concern of their contribution to the event and limited to ensure adequate power. Propensity score analysis may also be useful.
 - e. You should conduct sensitivity analyses to examine the robustness of the results to differing exposure and outcome definitions by repeating the main analyses for MCMs with different exposure and outcome definitions as you planned for OCs.
 - f. You should provide more details on the sensitivity analyses examining the potential effect of outcome misclassification on the prevalence ratio estimate for MCMs and the potential effect of an unmeasured confounder on study results.

12. It should be noted that analysis of secondary outcomes may have limited regulatory utility absent pre-specified statistical methods that are appropriate for the outcome assessed. Assessment of secondary outcomes would require multiplicity adjustments. Otherwise these secondary outcomes would be seen as exploratory in nature. The following are some general comments on the secondary outcomes:
 - a. You should provide the definition of the secondary study outcome of LBW.

- b. You should conduct additional analysis to compare the proportion of infants with LBW born to mothers exposed to TPM relative to the proportion of infants with LBW born to mothers not exposed to TPM.
 - c. The analyses on LBW should be adjusted for maternal age, race, smoking, and alcohol use.
13. You should provide justification for the signal definition of a relative risk greater than or equal to 5 in the exploratory study to assess the presence of signals for increased risk of MCMs.

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN
07/19/2011

MEMORANDUM OF TELECON

DATE: June 13, 2011

APPLICATION NUMBER: NDA 022580

DRUG NAME: Qnexa (phentermine/topiramate) capsule

BETWEEN:

Vivus, Inc.

Peter Tam, MBA – President

AND:

Division of Metabolism and Endocrinology Products

Eric Colman, M.D. – Deputy Director

Pooja Dharia, Pharm.D. – Regulatory Project Manager

BACKGROUND

Qnexa (PHEN/TPM) is a combination of two marketed products, phentermine and topiramate, indicated for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). It will be available in three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg.

A Complete Response letter was issued on October 28, 2010. An End of Review Conference was held on January 19, 2011 and follow-up meeting was held on April 14, 2011, during which an in-depth retrospective observational study of congenital malformations and birth weight in fetuses of women treated with topiramate for migraine prophylaxis was requested by FDA.

Vivus submitted the protocol for the observational study entitled, *OB-901 (FORTRESS): Fetal Outcome Retrospective study of TopiRamate ExpoSure Study* on May 27, 2011.

TELECONFERENCE

A teleconference was held to discuss two issues: (1) the FORTRESS study and (2) the pending advisory committee (AC) that will be held for Qnexa's second cycle.

Vivus stated that the FORTRESS study initially proposed four data sources for mother-infant dyads. One of the largest sources, HealthCore, with 800 dyads, recently pulled out of the agreement with Vivus. Vivus has continued to look for other sources and will provide an estimated 500 dyads with a replacement data source.. As a result of the net loss of 300 dyads, the study will be less powered than planned. The protocol submitted on May 27, 2011 had 90% power to rule out an increase in oral cleft risk by 5-6 fold for the 95% upper bound confidence interval. Vivus commented that they need feedback on the submitted FORTRESS protocol as soon as possible because finalizing the protocol is critical to continued viability of the program.

FDA stated that if Vivus included this information in writing it would be sent to the reviewers in OSE and biometrics who are reviewing the FORTRESS protocol. However, FDA noted that there would be no guarantee that the reviewers would be able to respond before the July 15th due date determined when the consults were initially sent to these two review divisions.

The logistics and timing of the second Qnexa AC were discussed. Vivus stressed the importance of holding the Qnexa AC prior to a general AC to discuss obesity drugs and cardiovascular (CV) safety, in order to eliminate potential bias against Qnexa's CV safety profile, as they felt the initial Qnexa AC was negatively biased by the preceding two days of discussion of CV safety of diabetes drugs. FDA commented that no date has been determined for the AC to discuss CV safety of obesity drugs, but an early 2012 time frame has been reported in the press. FDA reiterated its previous position that Vivus should target October 1, 2011, as the earliest time to resubmit the Qnexa NDA. This would likely result in a January 2012 AC meeting for the second Qnexa review cycle.

(b) (4)

Memo prepared by: Pooja Dharia, Pharm.D. - Regulatory Project Manager
Concurrence by: Eric Colman, M.D. – Deputy Director

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/s/

POOJA DHARIA
06/14/2011



NDA 022580

MEETING MINUTES

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your new drug application (NDA) dated and received December 28, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for QNEXA (phentermine/topiramate) Extended Release Capsule.

We also refer to your March 4, 2011, correspondence requesting a meeting to discuss the continued development of QNEXA.

A copy of the official minutes of the April 14, 2011 meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Guidance

Meeting Date and Time: Thursday April 14, 2011, 2:00 – 3:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 51, Conference Room: 1211
Silver Spring, Maryland 20903

Application Number: NDA 022580
Product Name: Qnexa (phentermine/topiramate)
Extended Release Capsule
Indication: Obesity
Sponsor/Applicant Name: Vivus, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Office of Drug Evaluation II

Curtis J. Rosebraugh, M.D., M.P.H. Director

Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy Egan, M.D.	Deputy Director for Safety
Mary Roberts, M.D.	Clinical Reviewer
David Carlson, Ph.D.	Pharmacology Toxicology Reviewer
Pooja Dharia, Pharm.D.	Regulatory Project Manager
John Bishai, Ph.D.	Safety Project Manager
Julie Marchick, MPH	Acting Chief, Project Management Staff

Office of Clinical Pharmacology

S.W. Johnny Lau, R.Ph., Ph.D.	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2 (DCP2)
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Office of Biostatistics

Mat Soukup, Ph.D.	Team Leader, Division of Biometrics 7 (DB7)
Ben Neustifter, Ph.D.	Mathematical Statistician, DB7

Office of Surveillance and Epidemiology

Jing (Julia) Ju, Pharm.D., Ph.D.	Pharmacoepidemiologist, Division of Epidemiology (DEPI)
Judy Staffa, Ph.D., R.Ph.	Acting Deputy Director, DEPI
Diane Wysowski, Ph.D.	Acting Epidemiology Team Leader, DEPI
Solomon Iyasu, MD, MPH	Director, DEPI
Tarek Hammad, MD, Ph.D.	Associate Director, DEPI
Joyce Weaver, Pharm.D.	Senior Risk Management Analyst, Division of Risk Management
Lanh Green, Pharm.D., M.P.H.	Safety Evaluator Team Leader, Division of Pharmacovigilance 1 (DPV1)
Selena Ready, Pharm.D.	Safety Evaluator, DPV1

Pediatric and Maternal Health Staff

Jeanine Best, MSN, RN, PNP	Senior Clinical Analyst
Karen Feibus, M.D.	Maternal Health Clinical Team Leader

Division of Neurology Products

Leonard P. Kapcala, M.D.	Senior Medical Officer
--------------------------	------------------------

SPONSOR ATTENDEES

Wesley W. Day, Ph.D.	V.P., Clinical Development (b) (6)
Malcolm McKay, Ph.D.	V.P. Regulatory Affairs and Corporate Compliance
Michael P. Miller, M.B.A.	Chief Commercial Officer
Craig Peterson, M.S.	Sr. Director, Clinical Development
Peter Tam, M.B.A.	President

(b) (6)

1.0 BACKGROUND

Qnexa (phentermine/topiramate) extended release capsules is a combination of two marketed products, phentermine and topiramate, indicated for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). NDA 22580 for Qnexa was submitted on December 28, 2009. The application provides for three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg.

On July 15, 2010, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss the safety and efficacy of Qnexa. When questioned about the approvability of Qnexa for the treatment of obesity in individuals with a BMI of ≥ 30 kg/m² or 27 kg/m² with weight-related co-morbidities, panel members voted unfavorably towards approval with a vote of 10 to 6. Major factors in their decision include significant safety risks such as teratogenicity and suicidality and lack of long-term data.

A Complete Response letter was issued on October 28, 2010. An End-of-Review Conference was held on January 19, 2011, during which an in-depth retrospective observational study of congenital malformations and birth weight in fetuses of women treated with topiramate for migraine prophylaxis was requested by FDA. Submission of this study is needed for continued development of Qnexa and to address the remaining deficiencies outlined in the Complete Response letter.

The purpose of this meeting was to discuss the feasibility of such a study and the ongoing drug development of Qnexa.

2. DISCUSSION

Your questions are repeated below, followed by our response in **bold** print and discussion in *italics*.

Feasibility Summary

1. Considering the number of mother-infant dyads available across the various database sources evaluated, does the Division agree that it is appropriate to conduct the retrospective observational study of pregnancy outcomes with topiramate using the Ingenix/I3/United Healthcare and Healthcore databases?

FDA Response: Based on the number of dyads identified from the databases that you explored, your argument (“because the vast majority of the identified dyads come from these two large databases, and because of methodological issues associated with combining data across numerous small and differently structured databases, VIVUS believes that limiting the retrospective observational study to the Ingenix and HealthCore databases provides the best approach.”) seems reasonable. However, these databases are not exhaustive of all databases that are available in the U.S. Other databases that contain large numbers of mother-baby dyads should

be explored before a final decision can be made on the most appropriate database(s) to use.

Responses sent by Vivus on April 13, 2011: We believe we have done an exhaustive search of the available U.S. databases and neither we nor our consultants are aware of any other databases that would be likely to yield large numbers of mother-baby dyads (see our next response regarding GPRD).

Is the Division aware of another database containing large numbers of mother-baby dyads that we have overlooked?

Discussion: FDA noted that there are other databases that might be explored for their usefulness, but FDA cannot direct the sponsor to particular data sources. The existence of contracts and agreements that FDA has with outside groups is publicly available information and may provide insight to the types of databases that may be acceptable.

If a single database can provide a large enough sample size to detect the relative risk of oral clefts at a reasonable level, it should be used to avoid statistical difficulties in combining different data sources, e.g. Ingenix and HealthCore. If a third database is identified with a large number of mother-baby dyads, but not large enough to be used alone, the use of this database along with Ingenix and HealthCore should be considered as that would increase the sample size and study power. As you stated in the protocol, the potential sample size (1,400 pregnancies with ≤ 100 mg /day topiramate exposure) in Ingenix and HealthCore combined may be able to exclude a relative risk of 6.2 with a study power of 80% (assuming exposed: unexposed ratio of 1:10 and 5% of type 1 error). However, it would be desirable to be able to identify a lower relative risk or to account for loss of study participants due to enrollment or eligibility criteria.

Responses sent by Vivus on April 13, 2011: We agree with your analysis and will strive to obtain as many dyads as possible.

Discussion: FDA encouraged the sponsor to submit a protocol for review and feedback.

We recommend that you keep exploring the feasibility of using other large healthcare claims databases that contain large numbers of mother-baby dyads. We also recommend that you should expand the study time period using the General Practice Research Database (GPRD) and explore the feasibility of using it, as the GPRD data used in your assessment was only 1985-2002, and could be made more current. The study results from GPRD, however, may not be generalizable to the U.S. population.

Responses sent by Vivus on April 13, 2011: We have recently confirmed that in Table 2 in our Feasibility Assessment document the results reported for GPRD included the most recently available data up to 2010, not 2002 as originally shown.

Discussion: No discussion occurred.

After you obtain the number of mother-baby pairs of interest in GPRD (with more recent years of data) and other potential databases in the U.S., we can better decide on the most appropriate database(s) to use to conduct the retrospective observational study of pregnancy outcomes with topiramate exposure.

Responses sent by Vivus on April 13, 2011: As stated above, the GPRD numbers reflect the currently available data. Among the publicly available databases, Ingenix and HealthCore were the largest. Our experts believe that we have evaluated the largest and best quality databases and are not aware of other databases that can substantially improve our ability to answer these questions.

Discussion: See FDA's suggestion above.

2. Does the Division agree that the primary objective/outcome of interest for the retrospective observational study is an evaluation of the frequency of oral clefts?

FDA Response: The primary objective/outcome of interest for the retrospective observational study should be the relative risk of oral clefts and other Major Congenital malformations (MCM) associated with topiramate exposure.

Responses sent by Vivus on April 13, 2011: When you state that the primary objective/outcome of interest should be "the relative risk of oral clefts and other Major Congenital malformations (MCM) associated with topiramate exposure," does the Division refer to; a) A single composite endpoint of oral clefts and other Major Congenital Malformations (MCM) or b) Two co-primary endpoints?

Discussion: FDA clarified that the two co-primary endpoints should be (1) oral clefts and (2) all MCM (including oral clefts).

3. Does the Division agree with the proposed (b) (4)

FDA Response: We disagree with the (b) (4) in the protocol. Our comments and recommendations are listed below.

- a. **We suggest that the primary objective/outcome of interest for the retrospective observational study should be the relative risk (instead of frequency) of oral clefts and other MCMs associated with topiramate exposure during the first trimester and during the 30 days preceding day 1 of the first trimester.**

Responses sent by Vivus on April 13, 2011: We agree with the Division that the outcome of interest is the relative risk and we agree it is important to capture all drug exposure peri-conception and we will provide a more detailed definition in the next draft of the protocol.

Discussion: No discussion occurred.

- b. We recommend adding an additional aim to examine the risk of oral clefts and other MCMs associated with topiramate for all doses and by specific dose during the first trimester and during the 30 days preceding day 1 of the first trimester.**

Responses sent by Vivus on April 13, 2011: As an additional aim, we agree to evaluate all doses and specific doses.

Discussion: No discussion occurred.

- c. In terms of study time, you propose to include women with a record of live birth from 2001 through 2010 in the study. We suggest that you extend the study time period from 1997 (first year when topiramate was available in the U.S. market) through 2010 if using a U.S. database. The study time period should start from the first year when topiramate was marketed in the U.K. through 2010 if using a U.K. database.**

Responses sent by Vivus on April 13, 2011: We agree to use all available data from the Ingenix and HealthCore databases. However, the availability of source medical records for outcome validation diminish the further one goes back in time. As indicated above, there were only 62 exposed mother-baby dyads in the GPRD database through 2010.

Discussion: No discussion occurred.

- d. You propose that the exposed group consist of all women with at least one pharmacy claim for any formulation of topiramate during days 0 to 100 within the 300 days preceding the date of a live birth at a dose of 100 mg or less. We believe that the proposed exposure criteria will not capture all women who had exposure to topiramate during their first trimester. Women who were dispensed topiramate prior to day 0 of the 300 days preceding the date of a live birth, but whose days of therapy fall within the range of 0 to 100 (defined as the first trimester) will not be captured as exposed. On the other hand, for preterm deliveries, the use of days 0 to 100 within the 300 days preceding the date of a live birth may incorrectly classify women who were exposed to topiramate before their first trimester of pregnancy as patients who had exposure during their first trimester. We recommend that gestational age, if available, should be used to classify the exposure status more accurately to minimize this misclassification bias. In both scenarios, the**

misclassification will bias the risk estimate towards the null hypothesis that there is no difference between exposed and unexposed women to topiramate during their first trimester of pregnancy.

Responses sent by Vivus on April 13, 2011: We acknowledge the importance of minimizing misclassification of time of exposure. As in other published studies using automated data evaluating the teratogenicity of drug, the gestational age at time of birth is not available. We propose to deal with this through sensitivity analyses varying definitions of first trimester.

Discussion: No discussion occurred.

- e. You should provide the time window for study outcomes to be identified, e.g. 90 days, or one year following the delivery date.**

Responses sent by Vivus on April 13, 2011: We agree with the Division and will define this in the protocol.

Discussion: No discussion occurred.

- f. We suggest that the control group of unexposed women should be a random sample of unexposed women who had the same obstetricians who delivered the exposed mothers. The ratio of unexposed to exposed should be at least 3:1.**

Responses sent by Vivus on April 13, 2011: We agree with the Division and this will be further defined in the protocol.

Discussion: No discussion occurred.

- g. You should provide a list of potential teratogens that you plan to capture during the first trimester of pregnancy in this study.**

Responses sent by Vivus on April 13, 2011: We will provide a list of teratogens in the protocol.

Discussion: No discussion occurred.

- h. We disagree with your proposal of performing a series of sensitivity analyses**

(b) (4)

Responses sent by Vivus on April 13, 2011: We are willing to perform a propensity score-adjusted analysis but are concerned about the limitations of this approach. For this reason our protocol will propose alternative analytical approaches to gauge whether any observed associations depend on the analytic method.

Discussion: No discussion occurred.

- i. We suggest that alcohol use and smoking status (as available) should be included in the analysis in addition to maternal diabetes and other comorbid conditions, other antiepileptic drug use, exposure to other known teratogens, and other important covariates. Appropriate statistical methods should be provided in an analysis plan.**

Responses sent by Vivus on April 13, 2011: We agree with the Division that the analysis should consider these and other potential confounders. The analysis plan will be further defined in the protocol.

Discussion: No discussion occurred.

- j. We agree that a subgroup analysis limited to patients with migraine will provide more information since it reduces the confounding by indication bias recognizing the sample size will be lowered. However, the subgroup analysis should be for patients with migraine at all doses, not just at daily dose of 100mg or less.**

Responses sent by Vivus on April 13, 2011: We agree with the Division and will define this in the protocol.

Discussion: No discussion occurred.

- k. You propose to use the HealthCore and Ingenix claims databases that contain 1,413 women with topiramate \leq 100 mg/day (807 women with migraine and topiramate \leq 100 mg/day) for this study. A control group of unexposed women of 14,000 will be used in the analysis. Assuming 5% of type 1 error, this sample size (1,400 exposed) may be able to exclude a relative risk of 6.2 with a study power of 80%, and a relative risk of 7.8 with a study power of 90%. Depending on the feasibility of using other databases and GPRD data for this study, the sample size may be larger than what you provided in using the HealthCore and Ingenix databases. It would be desirable to have a larger sample size to detect a smaller risk and to be able to examine all the study questions adequately.**

Responses sent by Vivus on April 13, 2011: We based our original power estimates on the assumption that we would only be including patients being treated with 100 mg or less, as previously recommended by the Division at our

End-of-Review meeting. As we plan to enlarge the sample size by including all indications and higher doses, we expect study power to increase.

Studies conducted using automated claims data typically involve efforts to validate outcomes against clinical records, and this is planned for the proposed study. We propose to report the study in two phases, by first producing a preliminary report based solely on automated data and then a final report with the validation results. We plan to submit an NDA for the full indication once the results from the claims-only analysis become available, with the final report to be completed while the NDA is under review.

Does the Division agree with this two-phase plan to submit epidemiology study results for the full indication?

Discussion: The sponsor clarified that the NDA for the full indication would be submitted contingent on a negative study. FDA clarified that data from a claims-only analysis would be considered preliminary data only, unless compelling data suggesting that the outcome codes had already been validated in the same or relevant data sources were provided.

Birth Weight

4. Is the birth weight data from the QNEXA clinical trial program adequate to address the FDA's concerns regarding birth weight?

FDA Response: No,

(b) (4)

Responses sent by Vivus on April 13, 2011: We do not believe a retrospective birth weight study is feasible because fetal and maternal weights are typically not available in automated claims data.

(b) (4)

[REDACTED] (b) (4)

Thus, VIVUS is proposing that the birth weight study be conducted [REDACTED] (b) (4)

Does the Division agree with this plan?

Discussion: FDA responded that birth weight data should be obtained using the clinical records used to validate outcomes in the retrospective MCM study. The birth weight data will provide useful information. The sponsor should include "small for gestational age" as an ICD-9 coding search term, using discharge summaries, in addition to their other proposed terms like "low birth weight."

[REDACTED] (b) (4)

5. Would the Division accept a resubmission of the QNEXA NDA for this [REDACTED] (b) (4) [REDACTED] in conjunction with the proposed REMS and [REDACTED] (b) (4) distribution program (Appendix 3)?

[REDACTED] (b) (4)

Responses sent by Vivus on April 13, 2011: Approximately half of the patients enrolled in the QNEXA development program met the criteria for the [REDACTED] (b) (4). There were 3 independent studies (OB-202/230, OB-204 and OB-303 – the largest phase 3 study) where the majority of the patients met the criteria for the [REDACTED] (b) (4) target population. Each of these studies independently showed the benefit-risk of QNEXA. Further, integrated analyses across the entire QNEXA development program showed similar efficacy and safety across gender and age sub-groups.

Given that teratogenicity is the remaining issue for the original NDA, VIVUS intends to resubmit the NDA for the [REDACTED] (b) (4) with the proposed REMS and [REDACTED] (b) (4) distribution. [REDACTED] (b) (4)

Could the Division clarify what is meant by "precedent setting"? If the review of our resubmission leads to discussions at higher Agency levels, we would appreciate the opportunity to participate in that process.

Discussion: Regarding timing of the NDA submission, FDA noted two upcoming issues: 1) preliminary results from an observational study reporting on teratogenicity and topiramate use should be publically available in August 2011.

2) A public FDA advisory committee meeting on a topic very relevant to a potential Qnexa REMS is expected to be held in late 2011. Because a second advisory committee meeting will be required for the assessment of Qnexa's response to the Complete Response letter, FDA requested that the sponsor resubmit the NDA no earlier than October 2011. This would allow sufficient time to review the resubmission and incorporate knowledge gained from the results of the expected observational study and REMS-related advisory committee and then have an advisory committee meeting to discuss the Qnexa NDA within a 6-month time frame.

The sponsor asked if the results of the teratogenicity study would sway FDA's view of teratogenicity with Qnexa (b) (4), if the study was sound. FDA responded that it is a possibility. However, FDA did not want to dissuade the sponsor from doing the efficacy and safety analyses (b) (4).

The sponsor also noted that in the case of a full indication approval of Qnexa, (b) (4). FDA responded that there is no way to be sure that the REMS program will be 100% effective.

FDA asked if the (b) (4) was approved, would the sponsor have the resources to support a cardiovascular outcome trial. The sponsor responded that the ability to conduct a CV outcome trial would be dependent on revenue stream. FDA responded that if there was a beneficial effect on CV outcomes with Qnexa treatment, this would favorably alter the risk/benefit assessment.

6. Does the Division agree with the proposed outline of the contents of the QNEXA NDA resubmission (b) (4) (Appendix 4)?

FDA Response: We will provide our thoughts regarding resubmission of the Qnexa NDA at that face-to-face meeting.

Responses sent by Vivus on April 13, 2011: This is the most urgent topic for our discussion.

Discussion: FDA agreed; see response to question 5.

7. With reference to the proposed table of contents (Appendix 4) of the resubmission does the Division consider the resubmission to be a Class 1 (2-month review) or a Class 2 (6-month review)?

FDA Response: The proposed resubmission would be classified as a Class 2 resubmission, with a 6-month review timeline. Please note that this application will be discussed at a second advisory committee meeting prior to the Division taking additional regulatory action.

Responses sent by Vivus on April 13, 2011: Understood.

Discussion: No discussion occurred.

3.0 ATTACHMENTS AND HANDOUTS

Responses sent by Vivus, Inc. on April 13, 2011.

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/s/

POOJA DHARIA
04/27/2011



NDA 022580

MEETING MINUTES

Vivus, Inc.
Attention: Peter Tam, MBA
President
1172 Castro Street
Mountain View, CA 94040

Dear Mr. Tam:

Please refer to your new drug application (NDA) dated and received December 28, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for QNEXA (phentermine/topiramate) Extended Release Capsule.

We also refer to your November 10, 2010, correspondence requesting a meeting to discuss the continued development of QNEXA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Review Conference

Meeting Date and Time: Wednesday January 19, 2011
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: NDA 022580
Product Name: Qnexa (phentermine/topiramate)
Extended Release Capsule
Indication: Obesity
Sponsor/Applicant Name: Vivus, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Office of Drug Evaluation II

Curtis J. Rosebraugh, M.D., M.P.H. Director

Division of Metabolism and Endocrinology Products

Mary Parks, M.D.	Director
Eric Colman, M.D.	Deputy Director
Amy Egan, M.D.	Deputy Director for Safety
Mary Roberts, M.D.	Clinical Reviewer
David Carlson, Ph.D.	Pharmacology Toxicology Reviewer
Todd Bourcier, Ph.D.	Pharmacology Toxicology Team Leader
Pooja Dharia, Pharm.D.	Regulatory Project Manager
Patricia Madara, M.S.	Regulatory Project Manager

Office of New Drug Quality Assessment

Joseph Leginus, Ph.D. ONDQA Reviewer

Office of Clinical Pharmacology

S.W. Johnny Lau, R.Ph., Ph.D. Clinical Pharmacology Reviewer, Division of
Clinical Pharmacology 2 (DCP2)

Sally Choe, Ph.D. Clinical Pharmacology Team Leader, DCP2
Justin Earp, Ph.D. Pharmacometrics Reviewer

Office of Biostatistics

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Mat Soukup, Ph.D. Team Leader, DB7
Ben Neustifter, Ph.D. Mathematical Statistician, DB7

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Judy Staffa, Ph.D., R.Ph. Acting Deputy Director, DEPI
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Lanh Green, Pharm.D., M.P.H. Safety Evaluator Team Leader, Division of Pharmacovigilance 1 (DPV1)

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Division of Neurology Products

Alice Hughes, M.D. Deputy Director for Safety
Leonard P. Kapcala, M.D. Senior Medical Officer
Norman Hershkowitz, M.D., Ph.D. Clinical Team Leader

Division of Advisory Committee and Consultant Management

Paul Tran, R.Ph. Health Science Administrator

SPONSOR ATTENDEES

Karen Benson, MBA, M.P.H. Sr. Associate, Regulatory Affairs
Charles H. Bowden, M.D. Sr. Director, Clinical Development

Wesley W. Day, Ph.D. V.P., Clinical Development

Malcolm McKay, Ph.D. V.P. Regulatory Affairs and Corporate Compliance
Michael P. Miller, M.B.A. Chief Commercial Officer
Craig Peterson, M.S. Sr. Director, Clinical Development

Meeting Minutes
January 19, 2011

Peter Tam M B A

President

(b) (6)

Barbara Troupin, M.D., MBA

Sr. Director, Medical Affairs

Leland F. Wilson, M.S.

Chief Executive Officer

(b) (6)

1.0 BACKGROUND

Qnexa (PHEN/TPM) is a combination of two marketed products, phentermine and topiramate, indicated for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). It will be available in three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg.

On July 15, 2010, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss the safety and efficacy of PHEN/TPM. When questioned about the approvability of PHEN/TPM for the treatment of obesity in individuals with a BMI of ≥ 30 kg/m² or 27 kg/m² with weight-related co-morbidities, panel members voted unfavorably towards approval with a vote of 10 to 6. Major factors in their decision include significant safety risks such as teratogenicity and suicidality and lack of long-term data.

A complete response letter was issued on October 28, 2010. The purpose of this End of Review conference is to discuss the continued development of Qnexa.

2. DISCUSSION

1. Is this comprehensive assessment of topiramate's and phentermine/topiramate's teratogenic potential adequate to enable resubmission of the NDA?

FDA Response: The mechanisms that contribute to topiramate-induced reproductive toxicity in non-clinical species remain incompletely defined. We do not agree that teratogenesis in mice administered topiramate is consistent with spontaneous background malformations, nor are we persuaded that teratogenesis in the additional two species, rats and rabbits, is a consequence of reduced body weight in the dams. The presence of teratogenesis in three species administered topiramate identifies a potential teratogenic hazard, but differences in species susceptibility and an incompletely defined mechanism precludes confidence in quantitatively assessing risk to human patients. In consideration of the existing animal and human data available for topiramate, it is unlikely that additional nonclinical studies would provide more than incremental information for human risk assessment.

Topiramate was approved for the prophylaxis of migraine headache in 2004. The recommended daily dose is 100 mg. Prescription data indicate a steady increase in the use of topiramate during the past seven years. A large percentage of this use is for migraine prophylaxis. Data from the North American Antiepileptic Drug Pregnancy Registry suggest an increased risk for major malformations and low birth weight in fetuses of women treated with a range of doses of topiramate. In particular, the relative risk for oral clefts was markedly increased in infants of women treated with topiramate compared with infants of women in the control group. In reference to these data, you remark in your briefing document that, "Further investigation is warranted since no conclusion can be drawn from such a small sample, and orofacial defects are one of the most prevalent US birth defects." We agree that further investigation would be useful.

To this end, we would like to discuss the feasibility of conducting a retrospective observational study of congenital malformations and birth weight in fetuses of women treated with topiramate for migraine prophylaxis.

Responses to your remaining questions are being deferred until we reach agreement on the feasibility of conducting the aforementioned observational study.

Discussion:

- *FDA began the discussion by citing the numbers of oral cleft defects and respective odds ratios from the U.K. (~12) and North American (~20) pregnancy registries. Because of the oral cleft data, FDA is uncomfortable moving ahead with approval of Qnexa. Despite efforts to minimize pregnancy during the Qnexa clinical trials, pregnancies still occurred. Moreover, during these clinical trials, women were given pregnancy tests every month, so duration of drug exposure to the developing fetuses was minimized in those women who became pregnant. Looking at existing health claims or electronic medical records databases linking women who used the 100 mg dose of topiramate for migraine prophylaxis to pregnancy outcome might provide a more precise estimate of risk of teratogenicity than data from epileptic women in whom the dosages of topiramate are generally higher and the duration of exposure to drug is longer.*
- *The sponsor questioned why there is a discrepancy between the incidence of major congenital malformations (MCM) in the control group of the North American Antiepileptic Drug Pregnancy Registry (NAAPR) (1.6%) and the March of Dimes (4%) and CDC (3%) control groups. FDA responded that the NAAPR has more stringent criteria for MCM than other registries. They exclude abnormalities such as chromosomal, biochemical abnormalities, and coincidental findings such as a single functioning kidney noted on ultrasound. All registries have different goals, case definitions and inclusion criteria and this is the reason it is difficult to compare them. FDA would like to look at the data in a structured way and research a database that better reflects the Qnexa patient population. The sponsor responded that the CDC registry also excludes the same abnormalities as NAAPR (Post-meeting Comment: It is FDA's belief that the sponsor was referring to the oral cleft abnormalities and not the overall major malformation rate. The CDC overall malformation rate of 3% includes chromosomal abnormalities.)*
- *The sponsor contended that a retrospective observational study was not feasible. Based on input from [REDACTED] (b)(4) in order to detect a two-fold increase in relative risk with 90% power, there would need to be ~19,000 exposed mother-baby pairs and ~80,000 unexposed mother-baby pairs. Based on a review of five available databases, the number of exposed mother-baby pairs was too low (4000). There were also several confounders (e.g. obesity and diabetes) that would need to be controlled, which would limit the conclusions. The sponsor suggested that any positive result therefore would be considered a false positive. FDA countered that any observational study trying to evaluate an association between a medication and birth defect would have similar challenges and these issues would not necessarily be*

prohibitive, especially in the case of Qnexa, where the relative risk of oral clefts is considered to be larger than 2, therefore requiring fewer subjects, and that 80% power is generally considered sufficient. An additional point raised was that the NAAPR director in the sponsor’s briefing package communicated that only 600 to 700 women exposed to a single anti-epileptic drug are needed to statistically identify a doubling of the baseline risk for physical birth defects.

- *FDA asked why we should not be concerned about the oral cleft and low birth weight data from U.K. and North American registries. The sponsor responded that there are reporting biases in the registries because they are collecting data from women with severe epilepsy. The prospective Qnexa registry proposed by the sponsor will reduce bias because it will have a matching control group of pregnant women not on drug. The sponsor also noted that one must balance empirical nonstatistical risk versus quantitative statistical benefit and the prospective study will provide the best picture of this.*
- *FDA questioned how long it will take to obtain robust data from a Qnexa pregnancy registry. The sponsor responded that it will be much faster to obtain data with a prospective study than retrospective. The retrospective study may give false positive results and take up to three years to complete. The sponsor stated that they have an incentive to complete the prospective study as quickly as possible in order to eliminate REMS requirements. They will also be providing monetary incentives to physicians and patients who comply with the pregnancy registry.*
- *To conclude, FDA stated that while a prospective study would provide information, given the current signal, we would not be comfortable approving the drug at this time even with the plan to minimize exposed pregnancies with a REMS. Unless proven otherwise through the conduct of scientifically sound, relevant feasibility studies, we believe that conducting an in-depth retrospective observational study of congenital malformations and birth weight in fetuses of women treated with topiramate for migraine prophylaxis is possible. The results of such a study will need to be submitted to FDA in order for the sponsor to move forward with the development of Qnexa and to address the remaining deficiencies outlined in the Complete Response letter issued on October 28, 2010.*

3.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The sponsor will submit a proposal for a retrospective observational study of congenital malformations and birth weight in fetuses of women treated with topiramate for migraine	Sponsor	N/A

prophylaxis, including the results of scientifically sound, relevant feasibility stud(ies) on which such a proposal is based.		
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5.0 ATTACHMENTS AND HANDOUTS

Slides sent by Vivus, Inc. on January 19, 2011.

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/s/

POOJA DHARIA
02/04/2011

MEMORANDUM OF MEETING MINUTES

APPLICATION: NDA 022580

DRUG NAME: Qnexa (topiramate/phentermine) capsule

SPONSOR: Vivus, Inc.

TYPE OF MEETING: Regulatory Briefing

MEETING DATE: August 20, 2010

TIME: 11:00 a.m. – 1:00 p.m. EST

MEETING CHAIR: Robert Temple, M.D., Deputy Center Director for Clinical Science

MEETING FACILITATOR: Lisa Lagowski, MN, RN-BC, CDER

MEETING RECORDER: Pooja Dharia, Pharm.D., Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

REGULATORY BRIEFING PANEL: (The list may be incomplete.)

Robert Temple, M.D., Deputy Center Director for Clinical Science
Solomon Sobel, M.D., Associate Director, Science and Research Staff
Issam Zineh, Associate Director of Genomics, Office of Clinical Pharmacology
Darrell Abernethy, Associate Director for Drug Safety, Office of Clinical Pharmacology
Robert O'Neill, Ph.D., Director, Office of Biostatistics
Julie Bietz, M.D., Director, Office of Drug Evaluation III
Charles Ganley, M.D., Director, Office of Drug Evaluation IV
Sally Choe, Ph.D., Clinical Pharmacology Team Leader
Kathleen Uhl, M.D., Deputy Director, Office of Medical Policy

FDA PRESENTERS:

Mary Roberts, M.D., Clinical Reviewer, DMEP

DIVISION OF METABOLISM AND ENDOCRINOLOGY REPRESENTATIVES:

Eric Colman, M.D., Deputy Director
Amy Egan, M.D., Deputy Director for Safety
Mary Parks, M.D., Director

OTHER FDA ATTENDEES: *See attached sign-in list*

Topic: Qnexa: for the treatment of obesity

Background

Qnexa (PHEN/TPM) is a combination of two marketed products, phentermine and topiramate, indicated for the treatment of obesity. Phentermine, approved in 1959, is indicated for the short-term treatment of obesity. Topiramate is approved for the treatment of epilepsy (1996) and migraine prophylaxis (2004). It will be available in three fixed-dose combinations of phentermine/topiramate: 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg.

On July 15, 2010, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss the safety and efficacy of PHEN/TPM. When questioned about the approvability of PHEN/TPM for the treatment of obesity in individuals with a BMI of ≥ 30 kg/m² or 27 kg/m² with weight-related co-morbidities, panel members voted unfavorably towards approval with a vote of 10 to 6. Major factors in their decision include significant safety risks such as teratogenicity and suicidality and lack of long-term data.

Meeting Objective:

The purpose of this regulatory briefing was to gain insight on the approvability of PHEN/TPM. In addition, potential risk evaluation and mitigation strategies were explored.

Discussion:

Panel and audience members asked several clarifying questions during the presentation by Dr. Roberts:

- Dr. Temple asked how it is known that both drugs contribute to weight loss, and not the individual component alone. Dr. Roberts answered that the sponsor conducted a study of the combination versus each component alone and there was a statistically significant greater weight loss of 3% with the combination. Dr. Temple further questioned whether the doses increase in sync; i.e. does each component contribute equally to weight loss as the dose increases? Dr. Roberts responded that both components contribute equally.
- An audience member asked whether there was fat loss. Dr. Roberts answered that the Phase 2 DEXA scans showed decreased fat mass, but the study did not look at visceral fat mass.
- An audience member asked about weight regain after discontinuing drug. Dr. Roberts answered of the subjects who discontinued the drug and lost at least 5% body weight the 40% of the weight lost was regained by 1 year.
- A panel member asked how many patients were on study drug at 12 months. Dr. Roberts answered that 61% of patients stayed on study drug for 12 months.
- A panel member asked about the mechanism of action of each drug. Dr. Roberts answered that phentermine is a stimulant that increases energy expenditure. The

mechanism by which topiramate causes weight loss is unknown. However, it is hypothesized that it alters taste and increases energy expenditure.

- Dr. Temple asked about the proposed cardiovascular trial. Dr. Roberts answered that this trial is not launched yet, but will have about 8,000 – 10,000 patients.
- Referring to Slide 48, an audience member asked how many of the patients in the 2010 North American Antiepileptic Drug pregnancy registry annual report were epileptics. Dr. Roberts replied that 85% were epileptics. Dr. Temple questioned whether there are increased abnormalities in epileptic women. Dr. Roberts replied that Dr. Lew Holmes (the director of the North American AED pregnancy registry) has stated that the cause of the abnormalities is not the disease (epilepsy) itself, but the antiepileptic drugs that are being taken during pregnancy. Dr. Uhl supported this by stating that the Lew Holmes database dispels the myth that epilepsy causes congenital malformations. Dr. Roberts added that congenital malformations seen in infants born to women with epilepsy may be confounded by the severity of the seizure (i.e. loss of consciousness) during the pregnancy.
- An audience member asked whether the drug precipitates in urine and whether it could precipitate in the fetus. Dr. Roberts did not have the answer to this question; however, an audience member later commented that one highly unusual case of congenital nephrolithiasis was found in the FDA Adverse Event Reporting System (AERS) database.
- Referring to Slide 53, Dr. Temple asked about the PHEN/TPM clinical trial development program. Dr. Roberts explained that about 5000 people have been exposed to PHEN/TPM throughout the entire clinical development program. About 70 – 80% of the patients were women. Of the Phase 2 studies, three were randomized, placebo-controlled trials. Of the Phase 3 studies, four were randomized, placebo-controlled trials. Dr. Temple asked if Dr. Roberts was concerned regarding the number of pregnancies in a clinical development program of this size. Dr. Roberts replied that she was based on the highly controlled requirements for double barrier or single barrier and OCP methods of contraception and negative monthly pregnancy tests. Dr. Uhl questioned how the patients were monitored during the clinical trial. Dr. Roberts replied that the patients were monitored with monthly pregnancy tests. Once the sponsor noted the significant occurrence of pregnancies, the informed consent process was updated and patients were reconsented. Dr. Temple commented that the Accutane iPLEDGE program still has pregnancy cases, despite its stringent monitoring program.
- Dr. Sobel asked if cognitive impairment was reversible. Dr. Roberts replied that it was reversible if PHEN/TPM is discontinued, but may persist while the patient stays on drug. The sponsor hoped that the phentermine would counteract topiramate's cognitive effects, but this did not occur, as was demonstrated with The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) testing which was done at 4 weeks

and 28 weeks. Language and attention deficits persisted at 28 weeks. The PHEN/TPM combination mirrored the effects noted with topiramate monotherapy.

- A panel member asked of the 26% of patients who withdrew from the study, did they have the same amount of weight loss? Dr. Roberts replied that the average weight loss was 10% after discontinuing drug.
- A panel member asked how the risk profile compared for the combination product versus topiramate alone. Dr. Roberts replied that the risk profiles look about the same; the safety concerns associated with the combination product are labeled side effects of phentermine and topiramate.
- A panel member asked why PHEN/TPM was discussed at the EMDAC. Dr. Roberts replied that since it was a new drug for obesity, DMEP wished to discuss their concerns in a public forum, including safety risks such as teratogenicity.
- Dr. Temple commented that of the 34 pregnancies occurred, 19 women delivered without any malformations. Dr. Roberts replied that these women were monitored monthly and discontinued drug early in pregnancy. In the real world setting, pregnancies may not be detected as early and fetal drug exposure may be longer. Irregular menstruation is common among obese women; these women may not realize they are pregnant and may continue to take the drug.
- Dr. Temple commented on the fact that the two drugs are readily available on the market. Dr. Roberts replied that if PHEN/TPM was approved, FDA would be able to track the safety issues and would be able to label the drug to mitigate risk. Dr. Zineh commented that if PHEN/TPM is not approved, it may underestimate the risk by not being able to monitor the drugs. The lowest doses currently available on the market are 15 mg of phentermine and 25 mg of topiramate.
- An audience member asked about the effects of treatment on glucose control. Dr. Roberts replied that in the Phase 2 trial for Type 2 diabetes mellitus patients, HbA_{1c} and weight loss was reduced by 0.6 percentage points and 7% respectively. The baseline HbA_{1c} requirement was 8.7. In the Phase 3 trial for obesity, HbA_{1c} was reduced by 0.3%. The mean baseline HbA_{1c} for this study was 6.7%.
- Dr. Temple questioned whether acidosis worsened bone status. Dr. Roberts commented that if PHEN/TPM is used in pediatric patients, the effect on their bone growth is unknown. Dr. Temple agreed that the effect on bone health should be evaluated.

PANEL DISCUSSION AND RESPONSES TO QUESTIONS:

Question 1: Based on the data presented, please list the following potential safety issues in descending order of concern (major adverse cardiac events, suicidality, metabolic acidosis, teratogenicity, and cognitive impairment).

Discussion/Clarification:

- Teratogenicity: Dr. Uhl commented that in the spectrum of birth defects, cleft defects are reversible. Another panel member commented that teratogenicity is an important consideration since the majority of patients will be women.
- Suicidality: There were no suicides; there was only an increase in suicidal thinking. However, with antiepileptic drugs as opposed to antidepressant drugs suicidality did not decrease with prolonged drug use.
- Cardiac events: A decision needs to be made whether a large cardiovascular outcomes trial should be required pre-marketing or post-approval.
- Metabolic acidosis/bone loss: Because the drug will be used in a largely female population, the effect on bone loss is important.
- Cognitive impairment: Cognitive impairment is reversible and not as much of a concern.
- Dr. Sobel commented that he would like to see second or third year data on the drug to see if weight loss plateaus. Safety risks may be tolerated if weight loss is sustained.

Question 2: If QNEXA is approved, please discuss your recommendations for minimizing pregnancy exposure and maximizing capture of exposed fetal outcome data.

Discussion/Clarification:

- A system similar to Accutane's iPLEDGE program can be ruled out since the two drugs are already out on the market.
- Dr. Zineh asked about time to pregnancy after ingestion of drug. If this is known, we may be able to figure out if the pregnancy was due to drug-drug interaction with oral contraceptives, or due to increased fertility because of weight loss.
- An audience member commented that in the case of the iPLEDGE program, patients were required to use two forms of contraception but patients usually did not adhere to this requirement. In addition, Accutane is used for the short-term. PHEN/TPM will be a chronic-use medication, posing more teratogenicity potential.

- Dr. Roberts commented on the sponsor's plan for a limited distribution program; i.e. five pharmacies will have the drug available; a select group of doctors will be able to prescribe it.

Question 3: Based on the heart rate and blood pressure data presented, please discuss if a cardiovascular outcome trial should be required pre-approval.

Discussion/Clarification: Dr. Temple recommended the cardiac outcomes trial be required post-approval, citing PHEN/TPM's efficacy over other marketed weight loss products. Dr. Zineh found the blood pressure and heart rate signals to be unremarkable.

Question 4: Dr. Temple requested that the following question be discussed by the panel: Should PHEN/TPM for the treatment of obesity be approved? Should obesity drugs have the same criteria as diabetes medications?

Discussion/Clarification: Dr. Zineh recommended approval with labeling. Dr. Sobel did not recommend approval because of the risks involved and the unknown benefit. Another panel member commented that the longer a woman stays on the drug, the more opportunities there are to become pregnant; he advised exploring the drug interaction between oral contraceptives and PHEN/TPM.

Attachments:

Slide presentation
Sign-in sheets

Minutes cleared by:
Eric Colman, M.D., Deputy Director
Amy Egan, M.D., Deputy Director for Safety

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
08/24/2010



NDA 022580

MEETING DENIED

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine/topiramate) controlled release capsule.

We also refer to your August 9, 2010, correspondence requesting a meeting to discuss the proceedings from the Endocrinologic and Metabolic Drugs Advisory Committee meeting. We are currently reviewing your application and internally discussing the items raised by the Advisory Committee panel members. At this point we do not know what action items will result from the August Regulatory Briefing. Therefore, we are denying this meeting request. If at a later date, we find that a meeting would be helpful, we will let you know.

If you have any questions, please call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	GI-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
08/11/2010

From: [Dharia, Pooja](#)
To: ["Malcolm McKay";](#)
Subject: Qnexa information request 8/10/10
Date: Tuesday, August 10, 2010 2:12:19 PM

Dear Malcolm,

Please see below for an information request for Qnexa:

This request pertains to the Division of Scientific Investigations' (DSI) inspection result for Study OB-109's bioanalytical reports of phentermine and topiramate, as well as the subsequent bioequivalence determination.

Upon inspection, DSI concluded the following:

- Data from analytical runs # 2 and 31 for Phentermine should be accepted and utilized in the bioequivalence evaluation (see discussion in 483 Item 1).
- Data of the 170 UISR samples prior to re-assay, coded as UISR in Table 6 "summary of re-assay for analytical reasons" of the bioanalytical report, should be accepted and utilized in the bioequivalence evaluation for Topiramate (see discussion in 483 Item 2).

Please respond to the following for Study OB-109 by August 20, 2010:

- Use analytical runs #2 and 31's plasma phentermine concentration data in evaluating phentermine bioequivalence for the phentermine/topiramate fixed dose combination capsules.
- Use the data for the 170 UISR samples prior to re-assay in evaluating topiramate bioequivalence for the phentermine/topiramate fixed dose combination capsules.
- Compare the phentermine and topiramate bioequivalence results between the two recommendations above to the reported phentermine and topiramate bioequivalence results.

Thanks,
Pooja

Pooja Dharia, Pharm.D.

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
08/10/2010

Executive CAC

Date of Meeting: August 10, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DDOP, Alternate Member
Todd Bourcier, Ph.D., DMEP, Team Leader
David Carlson, Ph.D., DMEP, Presenting Reviewer

Author of Minutes: David Carlson, Ph.D., DMEP

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 22-580

Drug Name: Phentermine + topiramate FDC (Qnexa)

Sponsor: Vivus, Inc.

Background

Phentermine Rat Carcinogenicity Study

The final study report of a GLP-compliant, standard two year oral (gavage) carcinogenicity study in Sprague-Dawley rats was reviewed and results were discussed at a meeting of the Executive Carcinogenicity Assessment Committee (ECAC). The study evaluated doses of 0, 3, 10, and 30 mg/kg and included an additional pair-fed vehicle control group. The study was considered acceptable based on previous concurrence with dose selection by the ECAC and results showing the high dose at or near the MTD due to excessive (34-41%) reduced body weight compared to controls (consistent with the intended pharmacodynamic effect). Phentermine did not reduce but in fact increased survival, consistent with reduced body weight in the treatment and pair-fed control groups.

Key study findings: There were no drug-related tumors in males or females at any dose tested. Numerical increases in uterine benign granular cell tumors and thoracic cavity combined benign and malignant hibernoma tumors in females were not considered biologically significant or treatment-related. NOAEL = 30 mg/kg/day (11X MRHD males, 18X MRHD females).

Executive CAC Recommendations and Conclusions:

- The Committee agreed the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded the study was negative for drug-induced carcinogenicity.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

NDA 22-580/Division File, DMEP
Todd Bourcier/Team leader, DMEP
David Carlson/Reviewer, DMEP
Pooja Dharia/PM, DMEP
ASeifried, OND IO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

ADELE S SEIFRIED
08/11/2010

DAVID JACOBSON KRAM
08/11/2010

2 hr (b) (4) and 6 hr (b) (4) was employed for setting the range of release. A (b) (4) width is not justified due to the low variability observed in the dissolution results.

If you have any questions, call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

MARY H PARKS
07/23/2010

From: [Dharia, Pooja](#)
To: ["Donna Kato"; "Malcolm McKay";](#)
cc: [Madara, Patricia;](#)
Subject: Qnexa information request 7/13/10
Date: Tuesday, July 13, 2010 11:13:49 AM

Hi Donna,

Please see information request below regarding Qnexa:

- Please update the ADRBANS.xpt for the RBANS Total Scale of Index Scores (Study OB-301, 5.3.5.1.25.3.1 analysis dataset).
- The variable PARAM includes Attention, Delayed Memory, Immediate Memory, Language and Visuospatial/Constructional but not Total Scale of Index Scores.
- In addition, the reference links for *Randolph C (1998a)* and *Randolph C (1998b)* point to the same pdf file (RBANS manual).
- Please update *Randolph C (1998b). RBANS: Stimulus Booklet A. Psychological Corporation, ...* in the link.

Please let me know if you have questions.

Thanks,
Pooja

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
07/13/2010

Madara, Patricia

From: Madara, Patricia
Sent: Sunday, July 04, 2010 5:56 PM
To: 'mckay@vivus.com'
Cc: 'Peter Tam'; Dharia, Pooja
Subject: NDA 22580 (Qnexa) Information Request

Importance: High

NDA 22580

INFORMATION REQUEST

Dear Dr. McKay:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine + topiramate) on December 28, 2009.

We are continuing to review your application and have a request for additional information. Please see the attached PDF file for details. Please submit the information officially to your NDA and reference this email in your response.

If you require additional clarification, please contact Dr. Pooja Dharia or me via email so that your questions can be easily forwarded to the appropriate reviewers. Thanks for your help with this.

Please confirm receipt of this email.

Sincerely,

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

**NDA 22-580 for Qnexa (Phen IR/Tpm ER) FDC Capsules,
15/92 mg, 11.25/69 mg, 7.5/46 mg, and 3.75/23 mg**

06/28/10

Biopharm Information Request:

The individual and mean dissolution data for topiramate used to construct Figure 2, p.13 of Module 32P22 (Drug Product), could not be located in the submission.

Therefore, you need to

- 1). Submit the above missing individual and mean dissolution data (the full profile) for topiramate of the 12 registration lots.

If you already submitted the needed information to the NDA, please provide the module, section, volume, and page Nos.

- 2). Based on the overall mean of these 12 lots, propose and resubmit the ranges (X% to Y% instead of NMT or NLT) of dissolution specifications at 0.5, 2, and 6 hrs for review. The proposed ranges should comply with FDA's IVIVC guidance (p.17), under "Setting Specifications Without IVIVC".

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

PATRICIA J MADARA
07/05/2010

From: [Dharia, Pooja](#)
To: ["Donna Kato";](#)
Subject: Qnexa information request 6/30/10
Date: Wednesday, June 30, 2010 9:15:52 AM

Hello Donna,

Please see the following information request for Qnexa:

Please explain the large proportion of subjects exposed to QNEXA >56 weeks when the studies were only to be 56 weeks in duration.

Thanks,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
06/30/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 28, 2010

TO: Pooja Dharia, Regulatory Project Manager
Mary Roberts, M.D., Medical Officer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-580

APPLICANT: VIVUS, Inc

DRUG: QNEXA (Phentermine/Topiramate)

NME: No

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: Treatment of obesity

CONSULTATION REQUEST DATE: March 5, 2010

DIVISION ACTION GOAL DATE: July 24, 2010
PDUFA DATE: July 23, 2010

I. BACKGROUND:

VIVUS, Inc. submitted NDA 22-570, a 505(b)(2) application for QNEXA, a combination of phentermine and topiramate, for the indication of treatment of obesity, including weight loss and maintenance of weight loss for obese patients (body mass index [BMI] > 30 kg/m²), or overweight patients (BMI >27 kg/m²) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity). Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The efficacy results of the studies are important in making a regulatory decision with regard to drug approval. Selection of sites was based on numbers of subjects enrolled at the site for the studies, the inspectional history of the highest enrolling clinical investigators, and the number of INDs in the DSI clinical trials database.

The protocols inspected included:

- A. OB-301 entitled “A Phase 3, Randomized, Double-Blind, Parallel-Design Study Comparing Multiple Doses of VI-0521 to Placebo and Their Single-Agent Phentermine and Topiramate Constituents for the Treatment of Obesity in Adults”
- B. OB-302 entitled “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Safety and Efficacy of VI-0521 in the Treatment of Obesity in an Adult Population with Body Mass Index equal to or greater than 35 kg/m²”
and
- C. OB-303 entitled “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Safety and Efficacy of VI-0521 in the Treatment of Obesity in Adults With Obesity-Related Co-Morbid Conditions.”

II. RESULTS (by Site):

Name of Clinical Investigator (CI) and Location	Protocol #/ # of Subjects screened/ randomized/ completed	Inspection Dates	Final Classification
Michelle Look, MD San Diego Sports Medicine 6699 Alvarado Rd, First floor Suite 2100 San Diego, CA 92120	OB 302 / 33/ 21 / 17 OB 303 / 33 / 27 / 23	May 13 to 25, 2010	Pending (Preliminary classification VAI)
Sam Miller, MD SAM Clinical Research Center 7711 Louis Pasteur Dr., Ste 300 San Antonio, TX 78299	OB 302 / 86 / 55 / 41 OB 303 / 91 / 59 / 39	May 24 to June 4, 2010	Pending (Preliminary classification NAI)
Fares Arguello Radiant Research Salt Lake City 448 East 6400 South Suite 200 Salt Lake City, UT 84107	OB 301/ 49 / 38 / 21	May 10 to 20, 2010	Pending (Preliminary classification VAI)
Mira Baron, M.D. Rapid Medical Research, Inc 3619 Park East Drive, Suite 300 Cleveland, OH 44122	OB 301/ 52 / 37 / 30	May 5 and 11, 2010	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = EIR has not been received and results are based on preliminary communications with the field.

1. Michelle Look, MD
San Diego Sports Medicine
6699 Alvarado Rd, First floor Suite 2100, San Diego, CA 92120

Note: Observations noted for this site are based on communications with the FDA investigator, review of the Form FDA 483, and review of the clinical investigator (CI) written response dated June 4, 2010. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** A total of 66 subjects were screened for the two studies conducted at this site. The subjects were screened and evaluated for inclusion into the appropriate study. For Protocol OB 302 at this site, 21 subjects were enrolled, and 17 subjects completed the study. A total of 12 subjects' records were audited. For Protocol OB 303 at this site, 27 subjects were enrolled, and 23 subjects completed the study. A total of 15 subjects' records were audited.

- b. **General observations/commentary:** The primary endpoint data were verified. A Form FDA 483 was issued for regulatory violations concerning failure to report an adverse event (AE) in Protocol OB 303 that was also the reason for withdrawal from the study. For Subject 049 randomized to the PHEN/TPM 7.5/46 mg arm, the adverse event of memory loss documented in the source documents was not recorded as an AE in the case report form and was not given as the reason for withdrawal. No other unreported adverse events were detected for either study. The CI responded in a letter dated June 4, 2010.
- c. **Assessment of data integrity:** Except for an isolated error, the audited studies appear to have been conducted adequately, and the data generated by this site for these studies may be used in support of the respective indication.

- 2. Sam Miller, MD
SAM Clinical Research Center
7711 Louis Pasteur Dr., Ste 300, San Antonio, TX 78299

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** A total of 177 subjects were screened for the two studies conducted at this site. The subjects were screened and evaluated for inclusion into the appropriate study. For Protocol OB 302 at this site, 55 subjects were randomized, and 41 subjects completed the study. A total of 20 subjects' records were reviewed. For Protocol OB 303 at this site, 59 subjects were randomized, and 39 subjects completed the study. A total of 21 subjects' records were reviewed.
- b. **General observations/commentary:** No regulatory violations were cited and no FDA Form 483 was issued. The primary endpoint data were verified. There was no evidence of under-reporting of AEs to the sponsor by the clinical investigator.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

- 3. Fares Arguello, MD
Radiant Research Salt Lake City
448 East 6400 South Suite 200, Salt Lake City, UT 84107

Note: Observations noted for this site are based on communications with the FDA investigator and review of the Form FDA 483. An inspection summary addendum will be

generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For Protocol OB 301 at this site there were 49 subjects screened, 39 subjects enrolled and 21 subjects who completed the trial. A total of 25 subjects' records were audited.
- b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under-reporting of AEs. A Form FDA 483 was issued for regulatory violations concerning the enrollment of 2 subjects who were taking gabapentin, an exclusionary criterion, and the use of testosterone, a prohibited medication, by one subject during the trial. These concomitant medications are documented in the NDA in Line Listing 16.2.4.4 "Prior and Concomitant Medications."
- c. **Assessment of data integrity:** Although isolated regulatory violations were noted, these are unlikely to importantly influence data reliability. In general, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Mira Baron, MD
Rapid Medical Research, Inc
3619 Park East Drive, Suite 300, Cleveland, OH 44122

- a. **What was inspected:** For Protocol OB 301 at this site there were 52 subjects screened and 37 subjects randomized. There were 30 subjects who completed the trial, although 2 of these subjects (Subjects 105-041 and 105-018) stopped study medication, they continued in the trial as documented in the line listings. There were no deaths or SAEs reported from this site. An in depth audit of the 25 subjects' records was performed.
- b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under-reporting of adverse events. Subject 105-012 had the dose reduced to every other day instead of being discontinued as required in the protocol. This reduction to every other day was performed with the knowledge of sponsor personnel and is documented in Data Listing 16.2.5.1 "Study Medication."
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites were inspected in support of this NDA. The primary endpoint data were verified. There was one AE of memory loss that was not reported to the sponsor by Dr. Look for Protocol OB 303, and thus, was not submitted in line listings to the NDA. This appears to have been an isolated occurrence. Violations noted at Dr. Arguello's site for Protocol OB 301 concerning the use of prohibited medications were documented in the data submitted to the NDA by the sponsor and are considered isolated in nature. Although some regulatory violations were noted as per above, these are considered isolated occurrences and are unlikely to significantly impact the integrity of primary efficacy and safety data overall.

Note: The final classifications for the inspections of Drs. Look, Miller and Arguello are pending. An addendum to this clinical inspection summary will be forwarded to the review division after a review of information from the Miller site or if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for these inspections.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

SUSAN LEIBENHAUT
06/29/2010

TEJASHRI S PUROHIT-SHETH
06/29/2010

From: [Dharia, Pooja](#)
To: [Donna Kato](#);
Subject: Qnexa information request 6/25/10
Date: Friday, June 25, 2010 10:00:30 AM

Good morning Donna,

Please see information request below for Qnexa:

Regarding the 1-year cohort:

1. Of the subjects with baseline history of depression or on anti-depressants at baseline, what number and percentage had a depression TME by treatment group?

2. Of the subjects without a baseline history of depression or on anti-depressants at baseline, what number and percentage had a depression TME by treatment group?

We would like to request a 1-week reponse timeline for these questions.

Thanks,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
06/25/2010

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, June 15, 2010 2:35 PM
To: 'Peter Tam'
Cc: Dharia, Pooja; Madara, Patricia
Subject: RE: NDA 22580 (Qnexa) Information Request
Importance: High
Attachments: 28May10 email req fo info.pdf

May 28, 2010 email attached.

From: Madara, Patricia
Sent: Tuesday, June 15, 2010 2:33 PM
To: 'Peter Tam'
Cc: Dharia, Pooja
Subject: NDA 22580 (Qnexa) Information Request
Importance: High

NDA 22580

INFORMATION REQUEST

Dear Peter:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine + topiramate) on December 28, 2009.

We are continuing to review your application and have the following requests for additional information. You may respond informally, via email, but also submit the information officially to your NDA and reference this email in your response.

- Please provide the range for the gestational age at pregnancy diagnosis? Please provide the mean and median for all study visits for placebo and PHEN/TPM treatment groups for studies OB-302, 303, and OB202/230.
- Provide a timeline for submission of your responses to the Information Request sent via email on May 28, 2010 (attached here).

If you require additional clarification, please contact Pooja Dharia or me via email so that your questions can be easily forwarded to the appropriate reviewers. Thanks for your help with this.

Please confirm receipt of this email.

Sincerely,
Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

6/15/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

PATRICIA J MADARA
06/15/2010

From: [Dharia, Pooja](#)
To: ["Donna Kato";](#)
cc: [Madara, Patricia;](#)
Subject: Qnexa CMC information request 6/8/10
Date: Tuesday, June 08, 2010 12:14:51 PM

Hello Donna,

Please see CMC information request for NDA 022580 Qnexa below:

1. Provide the dates of manufacture for all topiramate drug substance batches used in the preclinical, clinical and registration stability studies.
2. Provide a schematic drawing (with dimensions) for each capsule.
3. Justify the acceptability of a (b) (4) proportional increase in the proposed commercial batch size (b) (4) for VI-0521 Capsule compared to the largest batch size produced using the commercial manufacturing process (Registration batch of (b) (4) capsules).
4. Identify the lot numbers of phentermine hydrochloride and topiramate drug substances that were used to manufacture the drug product batches of PHEN/TPM capsules at the four different strengths identified in Section 3.2.P.5.4 – Batch Analyses.
5. Lower the acceptance criteria for Topiramate Related Compound A (TRCA) in the drug product specifications to 0.3%, which is its allowable level in Topiramate, USP. Results from drug product stability studies do not justify the proposed increase in TRCA levels above 0.3%.
6. Express the acceptance criteria for a) (b) (6) and b) (b) (6) in the drug product specification as “% w/w”, (b) (6)
8. Identify the lot numbers of the two batches of phentermine hydrochloride drug substance and three batches of topiramate drug

substance that were used to manufacture the registration stability drug product batches used in the drug product stability studies.

Thanks,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
06/08/2010



PREMATURE STUDY REQUEST

NDA 022580

Vivus, Inc.
Attention: Peter Tam, MBA
President
1172 Castro Street
Mountain View, CA 94040

Dear Mr. Tam:

Please refer to your new drug application (NDA) dated and received December 28, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Qnexa (phentermine and topiramate) Capsules

This submission included a request that FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act.

We have reviewed your proposed pediatric study request and are unable to issue a Written Request at this time. The Qnexa new drug application is still under review and a determination of safe use of Qnexa in adults should be made prior to issuing a Written Request for pediatric studies.

Therefore, we recommend that you resubmit your proposed pediatric study request following approval of Qnexa for use in adults.

Clearly mark your submission, "**PROPOSED PEDIATRIC STUDY REQUEST**" in large font, bolded type at the beginning of the cover letter of the submission.

We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at 301-796-5332.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	GI-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

ERIC C COLMAN
06/08/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, May 28, 2010 3:35 PM
To: 'Peter Tam'
Subject: NDA 22580 (Qnexa) Request for Information

Importance: High

NDA 22580

INFORMATION REQUEST

Dear Peter:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine + topiramate) on December 28, 2009.

We are continuing to review your application and have the following requests for additional information. Please submit the information officially to your NDA and reference this email in your response.

- Please provide the number and percentage of subjects with baseline depression or mood disorders for subjects in the 1-year safety cohort.
- Provide the number of subjects who were screened for studies OB-202/DM-230, OB-302, OB-303 separately and as a group and how many were excluded. Please give the number and percentages of reasons for exclusion (eg. include how many were excluded because the PHQ-9 score was too high, history of depression or mood disorder, suicidal behavior etc). Also, provide this information for OB-301.

If you require additional clarification, please contact me via email so that your questions can be easily forwarded to the appropriate reviewers. Thanks for your help with this.

Please confirm receipt of this email.

Sincerely,

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

PATRICIA J MADARA
05/28/2010

From: [Dharia, Pooja](#)
To: ["Donna Kato";](#)
Subject: Qnexa information request 5/7/10
Date: Friday, May 07, 2010 9:49:50 AM

Hi Donna,

NDA 022580
Vivus/Qnexa

As mentioned during our t-con yesterday, here's a summary of the information we requested:

1. **For the two cohorts 6-month and 1-year tables of low serum bicarbonate on drug (with 7 day window):**
 - a. **For serum bicarbonate <21 mEq/L and serum bicarbonate <17 mEq/L, Decrease from baseline in serum bicarbonate >5 mEq/L, please provide:**
 - Any visit post randomization**
 - At final visit (defined as last visit on drug)**
 - During titration phase**
 - During maintenance phase**
 - Persistence (2 consecutive or final visit)**
 - b. **For serum bicarbonate <21 mEq/L and <17 mEq/L, please subdivide by subjects taking or not taking metformin within 30 days of first abnormal bicarbonate value.**
 - c. **Please submit a Kaplan Meier curve of time to first occurrence of bicarbonate <21 mEq/L and time to first occurrence of persistence <21 mEq/L.**
 - d. **Please submit median time to onset of serum bicarbonate <21 mEq/L.**
2. **For the RBANS data submitted in OB-202 and OB-301, please submit the number and frequency of subjects divided by treatment**

group with index scores (immediate memory, visuospatial/ constructional, language, attention, delayed memory, and total scale) that decreased by 1.5 standard deviations.

3. Would you also be able to tell me when you plan on submitting the ECG datasets requested on April 16, 2010?

Thanks,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
05/07/2010

From: [Dharia, Pooja](#)
To: ["Donna Kato";](#)
Subject: NDA 22580 Qnexa Information Request 4/29/10
Date: Thursday, April 29, 2010 2:09:57 PM

INFORMATION REQUEST

NDA 22580

Dear Donna:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate) Controlled Release Capsules.

Please see below for an information request:

Please submit the complete NONMEM data files that were used to explore the covariate relationships for BMI, sex, ethnicity, race, renal function, age, concomittant drug administrations, and disease status for phentermine alone, topiramate alone, and both in combination. We are looking for a file that includes the NONMEM pharmacokinetic information and all the tested covariates in the relevant NONMEM format.

Please submit all documents officially to your NDA.

If you have any questions regarding the additional information requests, you can submit them via email and we will respond. **Please confirm receipt of this email.**

Sincerely,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
04/29/2010

From: [Dharia, Pooja](#)
To: ["Donna Kato";](#)
Subject: Information request 4/22/10
Date: Thursday, April 22, 2010 10:30:05 AM
Attachments: [Information request 4 22 10.pdf](#)

INFORMATION REQUEST

NDA 22580

Dear Donna:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate) Controlled Release Capsules.

I have attached a PDF document which includes an additional information request.

Please submit all documents officially to your NDA.

If you have any questions regarding the additional information requests, you can submit them via email and we will respond. **Please confirm receipt of this email.**

Sincerely,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

1. Please provide a subject profile of Subject 127-019 in Study OB-303.
2. For Subject OB-303 167-162, please provide the verbatim reason for discontinuation due to investigator discretion.
3. Please clarify the reason you define 3 months as 76 days and 6 months as 167 days, 9 months as 259 days, and 12 months as 350 days in the Extent of Exposure tables in the ISS.
4. Please give the location or provide the baseline and double-blind treatment phase numbers and frequencies of subjects in the ISS 6-MONTH and 1-YEAR cohorts across all treatment groups with regard to the following:

- Concomitant medications: in particular, cardiovascular/diabetic and psychiatric medications (antidepressants, antianxiolytics, antipsychotics). Please see below for examples.
- Medical conditions: in particular, hyperlipidemia, cardiovascular disease, hypertension, anxiety, depression, sleep disorders, and obstructive sleep apnea.
- Framingham risk scores

Diabetic medications: Any

- Metformin only
- Sulfonylurea only
- Metformin + sulfonylurea
- Other antidiabetic

- Alpha blocker
- Potassium-sparing diuretic
- Cardiac glycosides
- Statin

Cardiovascular medications: Any

- Antiplatelets (excluding aspirin)
- Aspirin
- ACE inhibitors
- Beta-blockers
- Nitrates
- Calcium channel blockers
- Thiazide diuretics
- Loop diuretics
- Fibrates
- ARBS

Psychiatric medications: Any

Antidepressants: Any

- SSRI
- Tricyclics
- Others (Bupropion)

Anxiolytics: Any

Antimanic: Any

Antipsychotic: Any

5. For each subject in the ISS cohorts that reported a Depression Subclass TME, please provide by treatment group the verbatim term qualifying as a Depression subclass TME and the corresponding PHQ-9 and C-SSRS responses obtained when the subject reported the TME.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
04/22/2010

From: [Chiang, Raymond](mailto:Chiang.Raymond)
To: ["McKay@vivus.com"](mailto:McKay@vivus.com)
Cc: [Zerislassie, Ermias](mailto:Zerislassie.Ermias); [Dharia, Pooja](mailto:Dharia.Pooja)
Subject: RE: whereabouts
Date: Friday, April 20, 2012 8:59:23 AM

Hi Malcolm,
Regarding your question below, see response from DMEPA/OSE.
thanks,
ray

Considering that the capsules are differentiated from one another by color and imprint of the strength as stated in the Package Insert Labeling, your proposal is acceptable. However, you need to plan an outreach to vendors, distributors, etc. to notify them of the change in the capsule appearance prior to your distribution of the batches with the proprietary name instead of "Vivus" on the capsule. Additionally, we recommend the addition of the statement on the container and carton labeling for a period of no longer than 6 months stating "New capsule appearance".

From: Malcolm McKay [<mailto:McKay@vivus.com>]
Sent: Tuesday, April 17, 2012 4:01 PM
To: Dharia, Pooja
Cc: Chiang, Raymond; Karen Benson
Subject: RE: whereabouts

Dear Pooja:

As a result of the trade name change for our drug product we have to discard our supply of capsules imprinted with "QNEXA".

VIVUS needs to order new capsules with which to produce launch materials and wanted to know if it was acceptable to FDA to place the word "VIVUS" on the capsule until such time as we obtain approval for a new trade name.

Assuming we are successful with a new trade name around the time of PDUFA, capsules with "VIVUS" would be on the market through December 2012, after which time they would be replaced with new batches of drug product with the new trade name on the capsule.

Thank you.

Sincerely,

Malcolm

From: Dharia, Pooja [<mailto:Pooja.Dharia@fda.hhs.gov>]
Sent: Tuesday, April 17, 2012 12:19 PM
To: Malcolm McKay
Cc: Chiang, Raymond
Subject: whereabouts

Hi Malcolm,

I will be out of the office starting Thursday 4/19 until next Monday 4/23. I will be back on Tuesday April 24th. Ray Chiang (cc'ed on this e-mail) will be covering for me and will be sending you the PI, if it is ready to go at the end of the week.

I also wanted to note that the last time you sent us back the PI, you did not track all the changes which makes it hard for us to know what you revised. Please make sure you use track changes for any edits you make.

Thanks!
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov <<mailto:pooja.dharia@fda.hhs.gov>>
(301) 796-5332

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/s/

RAYMOND S CHIANG
04/20/2012

Madara, Patricia

From: Madara, Patricia
Sent: Friday, April 16, 2010 10:44 AM
To: 'Donna Kato'
Cc: 'Peter Tam'; Dharia, Pooja
Subject: IND 68651 and NDA 22580 (Qnexa) INFORMATION REQUEST

Importance: High

IND 68651
NDA 22580

INFORMATION REQUEST

Dear Donna:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine + topiramate) and to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act on December 28, 2009.

In addition, we refer to your amendment to the IND, submitted on February 5, 2010, containing the final study report for your thorough QT study titled "*OB-118: A Phase 1 Randomized, Double-Blind, Placebo and Active-Controlled, Parallel Group/Crossover Thorough QT/QTc Study to Evaluate the Effect of a Therapeutic and a Supra- Therapeutic Dose of VI-0521 on Cardiac Repolarization in Healthy Male and Female volunteers.*" This study was referenced in your NDA.

We are currently reviewing this submission and have the following request for additional information:

- **Please submit Day 24 ecgs for double delta calculations, and update your raw data set EG.XPT to include Day 24 (VISITDY=24) ecgs for all groups.**

Please contact me if you have any questions. **Please confirm receipt of this email.**

Sincerely:

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-68651	ORIG-1	VIVUS INC	PHENTERMINE/TOPIRAMATE; VI-0521
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

PATRICIA J MADARA
04/16/2010

From: [Dharia, Pooja](#)
To: ["Donna Kato";](#)
Subject: NDA 22580 Qnexa information request 04/07/10
Date: Wednesday, April 07, 2010 11:13:43 AM
Attachments: [info request 4 7 10.pdf](#)

INFORMATION REQUEST

NDA 22580

Dear Donna:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate) Controlled Release Capsules.

I have attached a PDF document which includes an additional information request.

Please submit all documents officially to your NDA.

If you have any questions regarding the additional information requests, you can submit them via email and we will respond. **Please confirm receipt of this email.**

Sincerely,
Pooja

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

NDA 022580
Qnexa/Vivus/Information request
April 7, 2010

Please submit user manuals for the IWQOL-Lite and SF-36 instruments. In order to evaluate these instruments, we require you to submit more detailed materials for each instrument to support proposed claims. These materials include a conceptual framework of the instrument, content validity documentation, assessment of construct validity, reliability, and ability to detect change.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
04/07/2010

1. Please provide a narrative regarding the following patients with the adverse events of hallucination or euphoria.
 - OB 303-128-026 hallucination
 - OB 303-248-130 visual and auditory hallucination
 - OB 303-194-039 hallucination
 - OB-303-145-040 euphoria
 - OB-303-148-066 euphoric feeling
 - OB 202-0545 euphoria
2. Please provide the absolute and percent weight loss of subjects experiencing a biliary disorder, such as cholelithiasis, cholecystitis, and cholangitis, divided by treatment group.
3. Please clarify if the data in Tables 1, 2, 9, and 10 include only subjects currently on drug. If not, please revise Tables to include only subjects on drug or discontinued drug within 1 week. In addition, the information request sent on March 19, 2010 should also include subjects on drug.
4. Please provide further description (number and frequency) of the “other” reason for any change to study medication, using the following terms:
 - Other: not related to an adverse event and
 - Other: Related to an adverse event.Further describe the adverse event by a system organ class across all treatment groups for the 6 month and 1 year cohorts by number and frequency.

Example: Other Reason for Any Change to Study medication

Drug Holiday
Drug Tolerability
Event not related to Drug
Other
 Not related to AE
 Related to AE
 Ophtho SOC
 GI SOC
 Psychiatric SOC

5. In the Pregnancy source documents, please provide the treatment assignments in Table 1.0.

NDA 022580
Qnexa/Vivus/Information Request
April 6, 2010

6. Please clarify the discrepancy between the number of spontaneous abortions in Table 1.0 and miscarriages in Figure 1 of ISS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
04/06/2010



NDA 022580

INFORMATION REQUEST

VIVUS, Inc.
Attention: Peter Tam, M.B.A.
President
1172 Castro Street
Mountain View, CA 94040

Dear Mr. Tam:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate) Controlled Release Capsules.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your requests for a partial waiver and partial deferral of pediatric studies for this application. However, one of the requirements of a deferral request is that you submit a timeline for the completion of pediatric studies. Your submission does not contain an adequate timeline. Within 30 days of the date of this letter, submit a timeline that includes the following dates (month, day, year): (1) protocol submission; (2) study completion; and (3) submission of study reports. Once we have reviewed your requests, we will notify you if the partial waiver request or the partial deferral request is granted.

If you have any questions, call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

MARY H PARKS
03/26/2010

From: [Dharia, Pooja](#)
To: ["donna@regprofessional.com"](mailto:donna@regprofessional.com);
cc: [Madara, Patricia](#);
Subject: NDA 22580 Qnexa clinical pharmacology information request 3/19/10
Date: Friday, March 19, 2010 11:48:49 AM
Attachments: [Information request clin pharm 3 19 10.pdf](#)

INFORMATION REQUEST

NDA 22580

Dear Donna:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate) Controlled Release Capsules.

I have attached a PDF document which includes an additional information request regarding clinical pharmacology review issues.

Please submit all documents officially to your NDA.

If you have any questions regarding the additional info requests, you can submit them via email and we will respond. **Please confirm receipt of this email.**

Sincerely,

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

NDA 022580
Qnexa/Vivus/Information Request
March 19, 2010

Please provide the pulmonary arterial systolic pressures if obtained with the ECHOs in Study OB 201. We recommend you to do the following for potential clinical pharmacology review issues of NDA 22-580:

- Conduct an in vitro release experiment to demonstrate whether alcohol will affect QNEXA[®]'s delayed release mechanism of topiramate for efficacy concern.
- Justify the absence or difference of certain drug interactions information in the proposed QNEXA[®] label (Section 12) from those in the approved TOPAMAX[®] label, such as the absence of the statement "Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated." and the difference of antiepileptic drugs interaction information.
- Justify the rationales for the confounded sequential design of the drug interactions study (OB-107) such as sensitivity to detect drug interactions via multiple doses, lack of washout period, potential confounding factors (drug metabolizing enzymes and transporters), and sequence of drug administration.
- Address the pharmacological activities of both phentermine and topiramate metabolites.
- Address the chiral inversion potential for topiramate via metabolism since it has 4 chiral centers.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
03/19/2010

From: [Dharia, Pooja](#)
To: ["donna@regprofessional.com"](mailto:donna@regprofessional.com);
cc: [Madara, Patricia](#);
Subject: NDA 22580 Qnexa information request 3/19/10
Date: Friday, March 19, 2010 9:14:25 AM
Attachments: [Information request 3 19 10.pdf](#)

INFORMATION REQUEST

NDA 22580

Dear Donna:

My name is Pooja Dharia and I will be the new project manager for this NDA.

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate) Controlled Release Capsules.

I have attached a PDF document which includes an information request.

Please submit all documents officially to your NDA.

If you have any questions regarding the additional info requests, you can submit them via email and we will respond. **Please confirm receipt of this email.**

Looking forward to working with you.

Sincerely,

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
pooja.dharia@fda.hhs.gov
(301) 796-5332

For all trials included in the ISS, please provide the location or submit to the NDA the following for placebo and all specific treatments (including a column for “any QNEXA treatment”) of study medication in tabular format. If you would like to submit the proposed shells for feedback prior to conducting analyses for the following summary tables, we would be happy to review your proposed shells and provide feedback.

For all summary tabular analyses, please show all treatments (including any QNEXA treatment by combining results of different dose combination products) on the same page in landscape format to facilitate easy comparison of all treatments.

1. Number and incidence of subnormal serum potassium values (i.e., less than 3.5 mmol/L) at any time during the placebo-controlled study phase (including scheduled and unscheduled visits), at final visit, during titration phase, during maintenance phase, and for “persistence” i.e., < 3.5 for 2 consecutive visits or at final visit), across all treatments for OB 301, OB 302, OB 303, OB 202, and DM 230.
2. Number and incidence of markedly low serum potassium values (i.e., < 3.0 mEq/L and > 5 mEq/L decrease from pretreatment) at any time during the placebo-controlled study (including scheduled and unscheduled visits), at final visit, during titration phase, during maintenance phase, and for “persistence” (i.e., < 21 for 2 consecutive visits or at final visit), across all treatments for OB 301, OB 302, OB 303, OB 202, and DM 230.
3. Of subjects with subnormal serum potassium values (<3.5 mmol/L) how many were on a concomitant non-potassium sparing diuretic?
4. Number and incidence creatinine >100% from baseline at any time during the placebo-controlled study phase (including scheduled and unscheduled visits), at final visit, during titration phase, during maintenance phase, and for “persistence” i.e., creatinine >100% for 2 consecutive visits or at final visit), across all treatments for OB 301, OB 302, OB 303, OB 202, and DM 230.
5. Number and incidence of subnormal glucose values (i.e., less than 50 mg/dL) at any time during the placebo-controlled study phase (including scheduled and unscheduled visits), at final visit, during titration phase, during maintenance phase across all treatments for OB 301, OB 302, OB 303, OB 202, and DM 230. Please provide the mean weight loss of this group compared to subjects without hypoglycemia.
6. Provide the number and percentages of subjects requiring downward adjustments in hypoglycemic medication, anti-hypertensive medications across all treatment groups.

NDA 022580
Qnexa/Vivus/Information Request
March 19, 2010

7. Provide the number and percentages of subjects started on psychiatric medications (Antidepressants: SSRI, Tricyclics, Others such as Venlafaxine, Bupropion; Antianxiolytics: such as Lorazepam, Alprazolam, etc; Antimanic, and Antipsychotics) across all treatment groups.
8. Provide the number and incidence of subjects started on potassium supplements across all treatment groups.
9. Provide the number and incidence of subjects started on anti-insomnia medications including over-the-counter sleep aids across all treatment groups.
10. For the analysis in the ISS of the PHQ-9, do the scores reflect inclusion of Question 5?
11. Please provide the pulmonary arterial systolic pressures if obtained with the ECHOs in Study OB 201.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

POOJA DHARIA
03/19/2010



IND 068651
NDA 022580

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Vivus, Inc.
1172 Castro Street
Mountain View, California 94040

Attention: Peter Tam, MBA
President

Dear Mr. Tam:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Phentermine and Topiramate Controlled-release Capsules, 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg.

We also refer to your September 29, 2009, correspondence, received September 30, 2009, requesting review of your proposed proprietary name, Qnexa, and to your January 15, 2010, General Correspondence Amendment to NDA 022580, and received January 18, 2010. We have completed our review of the proposed proprietary name, Qnexa and have concluded that it is acceptable.

The proposed proprietary name, Qnexa, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Patricia Madara at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- IND-68651	----- ORIG-1	----- VIVUS INC	----- PHENTERMINE/TOPIRAMATE; VI-0521

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/s/

CAROL A HOLQUIST
03/05/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, March 05, 2010 12:42 PM
To: 'Donna Kato'
Cc: Dharia, Pooja; 'Peter Tam'
Subject: FW: NDA 22-580 120-Day Safety Update - CLARIFICATION - Please confirm receipt
Importance: High

Hi Donna;

Please see the Division's responses to your questions concerning the 120-day safety update. Please contact me if you have any questions.

Sincerely;

Pat Madara
 Regulatory Project Manager
 Division of Metabolism and Endocrinology Products
 Office of Drug Evaluation II
 Center for Drug Evaluation and Research
 10903 New Hampshire Avenue
 Silver Spring, MD 20993-0002
 Phone: 301-796-1249

From: Donna Kato [mailto:donna@regprofessional.com]
Sent: Friday, February 26, 2010 3:09 AM
To: Madara, Patricia
Cc: Peter Tam
Subject: NDA 22-580 120-Day Safety Update - CLARIFICATION - Please confirm receipt

Dear Pat,

We reference the Division's email of February 12, 2010 and VIVUS's email of January 26, 2010 (attached). Thank you for providing the Division's response to VIVUS's proposal for the 120-day safety update. The purpose of this email is to clarify our understanding of the Division's response. The Division's comments are in **bold** typeface followed by VIVUS's clarification in regular font.

There were only two studies that were not included in the original NDA. OB-204 is a single-center, 6-month proof of concept study conducted in 45 patients with sleep apnea (23 on placebo and 22 on QNEXA) that completed last patient, last visit on September 22, 2009 with the CSR in progress. The second study is OB-305, an ongoing, multi-center, double-blind, placebo controlled study consisting of subjects that completed one year treatment in OB-303. Patients in OB-305 remain randomized to their original treatment in OB-303. This study is intended to provide two year safety and efficacy data [REDACTED] (b) (4)

Please note that neither of these studies provide data that would add substantively to the existing summaries of the 6 month and 1 year experience as submitted in the original NDA. OB-204 would only add an additional 22 QNEXA patients treated for 6 months and OB-305 data is blinded since the study is ongoing.

VIVUS wishes to provide the following clarification and requests confirmation of our understanding of FDA's comments.

- 1. FDA: Please update the number of patients exposed to drug across all doses, the duration of drug exposure, demographics, discontinuations with reasons, and concomitant medications.**

VIVUS: The requested information will be provided separately for OB-204 as this study has been unblinded and the final

3/5/2010

report is in preparation. Study OB-305 is blinded since it is ongoing; however, as part of the 120-day update, overall exposure (showing cuts of exposure greater than 1 year), demographics, discontinuations with reasons and concomitant medications can be provided in a blinded manner. Please note that the total number of patients exposed by dose will not change as a result of OB-305 data, since these patients continued in their same treatment arm in OB-303.

Since OB303 is unblinded and OB305 is an extension study of OB303 with the same randomization, why can't Vivus submit the information in an unblinded manner? Also how are you planning to update drug exposure in a blinded manner?

2. FDA: The safety update should include discussions of TMEs and integrate the new information with what was presented in the NDA and what is requested below.

VIVUS: The 120-day safety update will include a summary of the TMEs observed in OB-204. These new TMEs will be described separately but in the context of the TMEs provided in the original ISS. VIVUS proposes that TME data from OB-204 will not be integrated with the data presented in the original NDA due to the small number of subjects treated with QNEXA (22). In addition, for OB-305, only the TMEs that occurred during OB-305 will be presented (information will not be integrated with that from OB-303). These TMEs will be described separately but in the context of the original ISS. **This is acceptable**

3. FDA: Narratives and CRFs, PHQ-9, C-SSRS are acceptable as proposed.

VIVUS: Thank you. Narratives and CRFs will only be provided for SAEs, drop outs due to AEs and deaths.

After further thought, please also provide narratives and CRFs for the PHQ-9 score ≥ 15 , subjects with a +PHQ-9 Question 9 and severe TMEs

4. FDA: All deaths, SAEs, and pregnancies should be listed. All source documents related to pregnancies should be submitted.

VIVUS: This information will be submitted for OB-204 (unblinded) and OB-305 (blinded).

Again if OB 303 is unblinded and OB 305 is an extension of the study with the same original randomization, why can't the data be sent unblinded?

5. FDA: A frequency table for SAEs, dropouts due to AEs, and TMEs should be submitted divided by the whole study, titration phase and maintenance phase.

VIVUS: This information will be submitted for OB-204. Information for OB-305 will be provided in a blinded manner. According to the design of OB-305, not all subjects have a titration phase. Only subjects who had their dose titrated down in the OB-303 study retain the option to have their dose titrated back up to the assigned dose in the extension study. Therefore, we cannot present the AE information by titration phase and maintenance phase for OB-305 as we did for OB-303. Adverse event data will be presented for the OB-305 study as a whole study, and the data will not be separated by titration phase and maintenance phase. We propose providing OB-204 safety information (eg, SAEs and AE discontinuations) for the whole study and not separated by titration and maintenance phase due to the small number of subjects in the study. TMEs for OB-204 and OB-305 will be summarized as stated in #2 above.

This is acceptable

Finally, please confirm the Division's agreement to VIVUS's proposal in the follow up email of January 27, 2010 concerning the electronic datasets:

Upon further consideration, VIVUS proposes that the datasets for each of the studies (OB-204 and OB-305) will not be submitted with the 120-day safety update but they can be provided with the final study reports. This will avoid any potential confusion caused by differences between the current in-process datasets and the final datasets that are produced for the final study reports.

This is acceptable

Concerning the additional requests made in the February 12, 2010 email, VIVUS will submit the proposed table shells for the Division's review in a separate correspondence.

Some of the additional requests (Questions 4, 5, 9, 11) do not require a tabular format. Responses to Questions 4, 5, 9, 11 and the proposed table shells for the remaining requests need to be submitted by March 10, 2010.

Thank you.

Donna Kato
VIVUS, Inc.

3/5/2010

(408) 857-4453

APPEARS THIS WAY ON
ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

PATRICIA J MADARA
03/05/2010



NDA 22580

FILING COMMUNICATION

Vivus, Inc.
Attention: Peter Tam, M.B.A.
President
1172 Castro Street
Mountain View, CA 94040

Dear Mr. Tam:

Please refer to your new drug application (NDA) dated and received December 28, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Qnexa (phentermine and topiramate) Capsules, 3.75mg/23mg, 7.5mg/46mg, 11.25mg/69mg, and 15mg/92mg.

We also refer to your submissions dated January 18, 2010 (2) and February 5, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 28, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 30, 2010.

During our filing review of your application, we identified potential review issues and have the following requests for additional information:

Clinical

Please provide the following information regarding the PHQ-9 questionnaire. Complete two analyses using the studies in the ISS 6 month and 1 year cohorts.

1. Number and incidence of subjects with a positive response to question 9 of PHQ-9 on two or more consecutive occasions or at final visit including all treatment doses as well as a column for "any PHEN/TPM"
2. Number and incidence of subjects with a PHQ-9 score of 10 or greater, 15 or greater, 20 or greater at any time post randomization, final visit, titration phase, maintenance phase including all treatment doses as well as a column for "any PHEN/TPM"
3. Number and incidence of subjects with a decline in the PHQ-9 of at least 5 points at any time post treatment, final visit, titration phase, maintenance phase including all treatment doses as well as a column for "any PHEN/TPM"

Additional information requests

4. Please provide the verbatim reasons for drug holidays, switch to QOD dosing, and drug reductions due to "drug tolerability" and "other" in a table format in the ISS for the 6 month and 1 year cohorts.
5. In the Post-text tables used for all Phase 2 and Phase 3 studies (eg OB 303 CSR Table 14.4.2.1) under the Action Taken column does DISCONTINATION refer to study medication discontinuation or study withdrawal?
6. Using the ISE 6 month and 1 year cohorts, please provide the definition of a "completer" and the location of a "completer efficacy analysis".

Note: We request submission of the above items within three weeks of receiving this letter. We request a response to the information request, Additional Requests section, dated February 12, 2010 (sent via email) by March 10, 2010.

7. Please provide subgroup analyses in the study report for gender, racial and age group for Studies 301, 302 and 303. Please report the treatment-by-subgroup interaction p-values.

Chemistry

1. Provide the letter of authorization for FDA to access DMF (b) (4)
[Redacted]
2. Lower the limit for a single unknown impurity in the drug substance phentermine HCl specification to the ICH identification threshold of 0.10%. See FDA's Guidance "NDAs: Impurities in Drug Substances".
3. Set the limits on (b) (4) in the drug product specification to the ICH qualification threshold of 0.5% each or provide qualification information in support of you (b) (4)

4. Indicate the location in the NDA of the dissolution profiles in different media in support of your proposed dissolution acceptance criteria.
5. Justify the lack of testing for (b) (4) in the product specification. We note that (b) (4) may be a quality issue for your product because your product specification includes limits for microbial, yeast, and mold counts, the primary bottle packaging includes a desiccant, (b) (4)
6. Justify the lack of common tests such as content uniformity, weight, size, hardness, friability, and (b) (4) in your in-process specifications of both the phentermine beads and the topiramate beads.
7. Note that, according to the official Pre-NDA meeting minutes of the 22-JUL-2009 meeting, FDA did not agree that your NDA be submitted with the proposed 3-month primary stability data.
8. Revise the draft labeling text to include the correct structure of phentermine hydrochloride.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies (b) (4) for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies (b) (4) for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Pooja Dharia, Regulatory Project Manager, at 301-796-5332.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

ERIC C COLMAN
02/26/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, February 12, 2010 3:08 PM
To: 'Donna Kato'
Cc: Peter Tam
Subject: RE: NDA 22-580, 120-Day Update
Importance: High
Attachments: 12Feb10 clin info request_safety update.pdf

INFORMATION REQUEST

NDA 22580

Dear Donna:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine and topiramate) Controlled Release Capsules.

I have attached a PDF document describing information required in your 120-day safety update. We are also including additional clinical requests for information so that you may begin to gather the data and submit it as soon as possible. These requests may also be sent to Vivus at a later date, via an official information request letter.

Please submit all documents officially to your NDA.

If you have any questions regarding the additional info requests, you can submit them via email and we will respond. If needed, a tcon providing clarification can be arranged. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Donna Kato [mailto:donna@regprofessional.com]
Sent: Thursday, February 11, 2010 12:11 PM
To: Madara, Patricia
Cc: Peter Tam
Subject: RE: NDA 22-580, 120-Day Update

Thanks Pat. Your assistance is much appreciated. I have been watching the news in disbelief of the record snowfall. Best to you all.

Donna Kato
VIVUS, Inc.

2/12/2010

(b) (6)

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Thursday, February 11, 2010 8:36 AM
To: Donna Kato
Cc: Peter Tam
Subject: RE: NDA 22-580, 120-Day Update
Importance: High

Hi Donna;

The federal government in the Washington D.C. area was closed most of last Friday and all of this week due to a record 3 foot snowfall and then a blizzard yesterday, dumping another 1 -2 feet of snow. Everything is way behind schedule. I will email the review team tomorrow to see if there is any final decision yet.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Donna Kato [mailto:donna@regprofessional.com]
Sent: Thursday, February 11, 2010 10:48 AM
To: Madara, Patricia
Cc: Peter Tam
Subject: RE: NDA 22-580, 120-Day Update

Hi Pat,

Based on our conversation last week on Feb 3, you expected to have a response from the review team on our proposal for the 120 day safety update. Have you received their input yet? The data cut for the database was Feb 3 and we would like to proceed with the analysis in order to meet the 120 day due date. Thanks for your help.

Donna Kato
VIVUS, Inc.

(b) (6)

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Wednesday, January 27, 2010 8:12 AM
To: Donna Kato
Cc: Peter Tam
Subject: RE: NDA 22-580, 120-Day Update

Hi Donna;

The Division and clinical review team are discussing your proposal. I should have a response by the end of this week or beginning of next week.

Sincerely;

2/12/2010

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Donna Kato [mailto:donna@regprofessional.com]
Sent: Tuesday, January 26, 2010 9:10 AM
To: Madara, Patricia
Cc: Peter Tam
Subject: NDA 22-580, 120-Day Update

Dear Pat,

VIVUS is planning for the 120-day safety update due April 27, 2009 and we wanted to get FDA's agreement on the content of this submission. The only clinical studies using VI-0251 that were ongoing at the time of the NDA submission (NDA 22-580, Dec 2009) were OB-305 and OB-204. OB-305 is a long-term extension study where patients from OB-303 continue blinded treatment for 1 additional year (up to 2 years total treatment duration) . This study is ongoing and the data are still blinded. OB-204 is a study in 45 obese patients with sleep apnea. This study was recently completed and data are being analyzed. The study titles are given below.

OB-204: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of VI-0521 for the Treatment of Obstructive Sleep Apnea/Hypopnea Syndrome in Obese Adults

OB-305: A Phase 3, Double-Blind, Placebo-Controlled, Multicenter Extension Study (From Study OB-303) to Determine the Safety and Efficacy of VI-0521 for the Long-Term Treatment of Obesity in Adults with Obesity-Related Co-Morbid Conditions

For the 120 day update, VIVUS proposes to summarize safety data from each study individually. From study OB-305, a blinded summary of clean (monitored) data that is entered into the database as of Feb. 3, 2010 will be included. In addition to tabular presentations of adverse events, laboratory shifts, PHQ-9 shifts, and C-SSRS results , VIVUS will include narratives and CRFs for SAEs, drop-outs due to AEs and deaths. For study OB-204, an unblinded summary of similar safety data will be included.

For Datasets, VIVUS proposes to submit SDTM data, annotated CRF and define.xml for each study individually (data will not be integrated with data originally submitted in the NDA).

Please let me know if this proposal is acceptable. We would appreciate the Division's input as soon as possible.

Donna Kato
VIVUS, Inc.

(b) (6)

For the safety update:

Please update the number of patients exposed to drug across all doses, the duration of drug exposure, demographics, discontinuations with reasons, and concomitant medications.

The safety update should include discussions of TMEs and integrate the new information with what was presented in the NDA and what is requested below.

Narratives and CRFs, PHQ-9, C-SSRS are acceptable as proposed.

All deaths, SAEs, and pregnancies should be listed. All source documents related to pregnancies should be submitted.

A frequency table for SAEs, dropouts due to AEs, and TMEs should be submitted divided by whole study, titration phase, and maintenance phase.

Additional Requests:

For all trials included in the ISS, please provide the location or submit to the NDA the following for placebo and all specific treatments (including a column for “any QNEXA treatment”) of study medication in tabular format. If you would like to submit the proposed shells for feedback prior to conducting analyses for the following summary tables, we would be happy to review your proposed shells and provide feedback.

For all summary tabular analyses, please show all treatments (including any QNEXA treatment by combining results of different dose combination products) on the same page in landscape format to facilitate easy comparison of all treatments.

Please submit the outlier criteria for laboratory values and vital signs as soon as possible, so that follow-up requests may be made.

1. Number and incidence of subnormal serum bicarbonate values (i.e., less than 21 mEq/L) at any time during the placebo-controlled study phase (including scheduled and unscheduled visits), at final visit, during titration phase, during maintenance phase, and for “persistence” i.e., < 21 for 2 consecutive visits or at final visit), across all treatments for OB 301, OB 302, OB 303, OB 202, and DM 230.
2. Number and incidence of markedly low serum bicarbonate values (i.e., < 17 mEq/L and > 5 mEq/L decrease from pretreatment) at any time during the placebo-controlled study (including scheduled and unscheduled visits), at final visit, during titration phase, during maintenance phase, and for “persistence” (i.e., < 21 for 2 consecutive visits or at final visit), across all treatments for OB 301, OB 302, OB 303, OB 202, and DM 230.

3. Of subjects with persistence (patients with 2 consecutive bicarbonate levels <21 or at final visit) of low serum bicarbonate, please provide in tabular form the number and frequency of adverse events by SOC and preferred term for these individuals, please subdivide this category into subjects taking concomitant metformin and those who were not taking metformin within the previous 30 days.
4. Please provide information on how BP and heart rate were collected in all the Phase 3 trials and Phase 2 trials and if there were specific procedures for collecting these vital signs in each study. Were they in supine or sitting position?
5. Please provide the outlier criteria used for all labs and vital signs
6. Please provide corrected QT interval data by using the Bazett's and Fridericia's formulas. In addition, please provide the number and frequency of subjects with a corrected QT >500 msec, corrected QT >30 msec from baseline, corrected QT >60 msec from baseline across all treatments and divide into titration phase, maintenance phase, and final visit.
7. Please provide targeted medical event frequency according to different ranges of number of AEs per subject basis across all treatments (including all combined QNEXA doses): 1 event/subject, 2-5 events/subjects, 6-10 events/subject, >10 events/subject
8. Please provide mean change, placebo-subtracted mean change, mean percent change from baseline in heart rate in whole double-blind treatment phase, titration phase, and maintenance phase across all treatment groups.
9. Provide all source documents related to the pregnancies, including newborn physical exams, any genetic reports from early terminated pregnancies, which occurred during the clinical development of Qnexa.
10. For the targeted medical events (TMEs) please provide tabular summaries showing the incidence of TMEs at any time during the whole study, during the titration phase, during the maintenance phase and persisting from the titration phase into the maintenance phase (i.e., onset during titration phase and persistence into maintenance phase for > 7 days)
11. Please provide the incidence of Hy's laws cases across all treatments for all placebo-controlled trials included in the ISS. Refer to the agency's [guidance](#) on Drug induced liver injury: premarketing clinical evaluation.
12. Please provide the mean absolute change from baseline, mean percent change, mean placebo-subtracted change, and mean placebo-subtracted percent change in bone mineral density at the lumbar spine, total hip, and femoral neck at the 1 year visit from the DEXA substudy.

- a. Please provide 2 separate analyses of the subgroups of patients with DEXA scans who experienced : 1) the adverse event of metabolic acidosis by preferred term; and 2) serum bicarbonate < 21 mEq/L and the differences (described above) in bone mineral density from placebo group and treated subjects who did not develop metabolic acidosis.
13. Provide the number and frequency of subjects that experienced dosage reduction, failure to up-titrate, or interruption of drug treatment
14. Please add the target medical event of oligohydrosis and hyperthermia: The preferred terms include decreased sweating, fever, hot flushes, dehydration, abscess, sweating increased, skin disorder, and flushing

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

PATRICIA J MADARA
02/26/2010



NDA 22580

NDA ACKNOWLEDGMENT

Vivus, Inc.
Attention: Peter Tam, M.B.A.
President
1172 Castro Street
Mountain View, CA 94040

Dear Mr. Tam:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Qnexa (phentermine and topiramate) Controlled Release Capsules

Date of Application: December 28, 2009

Date of Receipt: December 28, 2009

Our Reference Number: NDA 22580

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 26, 2010, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22580	ORIG-1	VIVUS INC	QNEXA (phentermine IR + topiramate modified release) CAPSULE; VI-0521

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/s/

PATRICIA J MADARA
01/08/2010

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, December 30, 2009 4:04 PM
To: Peter Tam
Subject: NDA 22580 Qnexa - Information Request

Importance: High

**NDA 22580
REQUEST**

INFORMATION

Dear Peter:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Qnexa (phentermine + topiramate) on December 28, 2009.

We are initiating our review of your NDA and have the following request for additional information. Please respond promptly, in writing, so that we may proceed with our evaluation of your application.

- Please provide tables listing all investigators - one for those who have financial information to disclose and one for those who do not.
- The tables should also include site (including country), number of patients screened, number of patients enrolled, number of protocol violations (major and other), number of protocol deviations, number of patients who completed the trial, and for the table with financials, the amount of money received and in what form (speaker's fees/cash/stock, etc.).

Please submit the information officially to your NDA and reference this email in your response.

If you require additional clarification, please contact me via email so that your questions can be easily forwarded to the appropriate reviewers. Thanks for your help with this.

Please confirm receipt of this email.

Sincerely,

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22580	----- ORIG-1	----- VIVUS INC	----- QNEXA (VI-0521) IR CAPSULE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA J MADARA
12/30/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 68,651

MEETING MINUTES

Vivus, Inc.
Attention: Peter Tam, M.B.A.
Chief Operating Officer
1172 Castro Street
Mountain View, CA 94040

Dear Mr. Tam:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VI-0521 (phentermine + modified release topiramate).

We also refer to the meeting between representatives of your firm and the FDA on July 22, 2009. The purpose of the meeting was to discuss provide guidance related to submission of a new drug application (NDA) for VI-0521.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: meeting minutes
Vivus response to pre-meeting minutes
Vivus handout
REMS template



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 22, 2009; 1 PM Eastern time
Meeting Location: Building 22, White Oak Campus, Silver Spring, MD

Application Number: 68,651
Product Name: VI-0521 (phentermine and topiramate)
Indication: treatment of obesity
Sponsor/Applicant Name: Vivus, Inc

Meeting Chair: Eric Colman, M.D.; Deputy Director
Meeting Recorder: Patricia Madara

FDA ATTENDEES

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy Egan, M.D., MPH	Deputy Director for Safety
Julie Golden, M.D.	Medical Officer
Ilan Irony, Ph.D.	Clinical Team Leader, Diabetes
Todd Bourcier, Ph.D.	Preclinical Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D.	Preclinical Pharmacology/Toxicology Reviewer
Patricia Madara, M.S.	Regulatory Project Manager

Office of Biostatistics; Division of Biometrics II

Todd Sahlroot, Ph.D.	Deputy Director
Janice Derr, Ph.D.	Statistical Reviewer @ DMEP

Office of Biostatistics; Division of Biostatistics VI (Quantitative Safety and Pharmacoepidemiology Division)

John Yap, Ph.D.	Statistical Reviewer for Safety
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Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Sally Choe, Ph.D.	Clinical Pharmacology Team Leader
Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer
Justin C. Earp, Ph.D.	Pharmacometric Reviewer

Office of New Drug Quality Assessment; Division of Pre-Marketing Assessment I

Suong Tran, Ph.D. CMC Lead, Branch 2
Elsbeth Chikhale, Ph.D. Chemistry Reviewer, Branch 2

Office of the Commissioner; Controlled Substance Staff (CSS)

Katherine Bonson, Ph.D. Pharmacology Reviewer

Office of Surveillance and Epidemiology

Mildred Wright, R.N., MSN Consumer Safety Officer; Review Management Staff

EXTERNAL ATTENDEES

Vivus Company Participants:

Karen Benson, M.B.A, M.P.H.	Sr. Regulatory Affairs Associate
Charles Bowden, M.D.	Sr. Director, Clinical Development
Ted Broman	Sr. Director, CMC
Wesley Day, Ph.D.	V.P., Clinical Development
Craig Peterson	Sr. Director, Clinical Research
Peter Tam, M.B.A	Chief Operating Officer
Barbara Troupin, M.D., M.B.A.	Sr. Director, Clinical Development

Consultants:



1.0 BACKGROUND

VI-0521 is a fixed dose combination (FDC) product of a new formulation of phentermine and controlled release topiramate being developed for the long-term treatment of obesity. Vivus, Inc is currently completing the phase 3 clinical trials for VI-0521 and plans to submit an NDA by the end of 2009. The purpose of this meeting was to obtain guidance from FDA on the overall format, structure and content of the NDA. On June 19, 2009, Vivus submitted a briefing document containing specific questions related to their NDA submission. FDA issued pre-meeting minutes on July 21, 2009. Based on the responses to Vivus's questions, the company requested further discussion on:

- Regulatory question #7
- Quality questions #3 and 6
- Clinical questions # 1, 3, 4, and 8
- Additional clinical comments; bullet #7
- Additional clinical pharmacology comments; bullet #4

All the questions and pre-meeting comments are in regular font while the meeting discussion is in **bolded font**.

Regulatory Question 1:

Does the Division agree that the NDA/eCTD for VI-0521 for treatment of obesity may be submitted as an application under FD&C Act Section 505(b)(2)?

FDA Response:

Yes. Please note the following new links for 505(b)(2) guidance documents:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>

<http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>

If you have any questions regarding User Fees, we urge you to contact Mike Jones in the Office of Regulatory Policy at 301-796-3602.

Meeting Comment: No further discussion

Regulatory Question 2:

Is the overall content and organizational structure of each Module given in the Table of Contents acceptable for an NDA/eCTD filing (reference Section 12.0)?

FDA Response:

Yes.

Meeting Comment: No further discussion

Regulatory Question 3:

Would the reviewers find a demonstration of the reviewability of Module 3 Quality and Module 4 Nonclinical Study Reports helpful, after the pre-NDA meeting?

FDA Response:

All disciplines (including Clinical – Module 5) may find a demonstration helpful.

Meeting Comment: No further discussion

Regulatory Question 4:

For the NDA/eCTD for VI-0521 (Qnexa™) would the Division prefer to have full copies of the Regulatory Correspondence included (Module 1.6 Meetings and 1.12 Other Correspondence) or will cross references to the location of the correspondence in the IND 68,651 (b)(4) be sufficient?

FDA Response:

Full copies in the NDA are preferred.

Meeting Comment: No further discussion

Regulatory Question 5:

Is the separate submission of the request of a waiver for the pediatric studies acceptable? [Note: The sponsor is now asking for a deferral for patients ages 12-17 and a partial waiver for patients 0- (b)(4)]

FDA Response:

Yes, but it must arrive prior to the 60-day filing date.

In accordance with section 505B(a)(3)(A) of the FDCA, the request for deferral must include the pediatric plan (a description of the planned or ongoing studies), certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

Meeting Comment: No further discussion

Regulatory Question 6:

Will the FDA comment on their expectations regarding Label Comprehension Studies?

FDA Response:

There are no regulations or Agency Guidance with regard to conducting Label Comprehension Studies on Medication Guides.

It is recommended that Medication Guides be written at a Flesch Kinkaid 6th to 8th grade reading level, and have a Flesch Reading Ease score of at least 60%. It is also recommended that fonts

such as Arial, Verdana, or APFont be used to make medical information more accessible for patients with low vision.

The Medication Guide must meet the Regulations as specified in 21 CFR 208.20. You are also referred to the FDA's Guidance for Useful Written Consumer Medication Information (published July 2006) for additional information.

Meeting Comment: No further discussion

Regulatory Question 7:

Does the Division agree with VIVUS' plan to request a categorical exclusion for environmental analysis (EA) for VI-0521?

FDA Response:

We will review your request for a categorical exclusion for environmental analysis and determine if it is acceptable.

Meeting Comment:

FDA indicated that the calculation will be required in the NDA submission. If the calculation shows that the estimated concentration of each active will be higher than the allowed amount in the regulations, the sponsor should proceed with the full environmental analysis.

Clinical

Clinical Question 1:

Does the Agency agree with VIVUS' plan for data pooling for the ISS as outlined above and detailed in the SAP in Appendix 6?

FDA Response:

Statistics:

- Yes, we agree with the proposal of having two cohorts (six months and one year) and the pooling of the three Phase 3 and two Phase 2 studies for the integrated summary of safety (ISS).
- With regards to "Adverse Event Counting Rules", we recommend that all analysis tables clearly specify when such rule is applied. In the SAP, at the system organ class level, please specify how the adverse events are chosen when multiple ones are reported with the same severity level.
- Please review Appendix Z regarding the contents of the Safety Analysis Plan and incorporate components that have yet to be addressed in the SAP.

Clinical:

- Please see the first comment under 'additional clinical comments'.

- Any safety information available at the time of filing [REDACTED] (b) (4) should be included in the ISS.

Meeting Comment:

The Division reiterated that they were interested in any pregnancies that had occurred. The firm commented that there had been 32 pregnancies across the entire development program and these had been followed to term.

Vivus questions in response to the pre-meeting minutes:

- Does the Division agree that the ISS SAP will cover the components outlined as applicable by the Division in the QSAP?

FDA Meeting Response:

Yes.

- Does the Division agree that our presentation of TMEs as amended in clinical question 5, adequately addresses adverse events of special interests?

FDA Meeting Response:

Yes.

Clinical Question 2:

Does the Agency agree with VIVUS' plan for data pooling for the ISE as outlined above and detailed in the SAP in Appendix 7?

FDA Response:

Statistics:

- Yes, we agree with the proposal to integrate the efficacy results from the one-year results of two Phase 3 studies, OB-302 and OB-303, in the integrated summary of efficacy (ISE). We recommend that statistical analysis models of the integrated database include "study" as a model factor.

Clinical:

- Please see the first comment under 'additional clinical comments'.

Meeting Comment: No further discussion

Clinical Question 3:

Does the Agency agree with VIVUS' plan regarding the format of the clinical data components for the VI-0521 NDA/eCTD?

FDA Response:

Statistics:

- Yes, it is acceptable to submit CDISC SDTM data for the three Phase 3 studies OB-301, OB-301 and OB-303, the ISS and ISE, and the Phase 1 study OB-118. However, we request that you also submit CDISC STDM data for the four Phase 2 studies OB-201, OB-202, DM-230, and DM-231. We note that the data sets for the ISS from these studies will be submitted in the CDISC STDM format. Please refer to Appendix Z regarding Study Data Tabulation Model (SDTM) and MedDRA.

Clinical Pharmacology:

- Your plan is acceptable.

Meeting Comment: No further discussion

Clinical Question 4:

Does the Agency agree that analysis datasets will be submitted only for those studies whose analysis plans require substantive data derivations?

FDA Response:

Statistics:

- Yes, it is acceptable to submit analysis datasets for studies with statistical analysis plans that involve substantive data derivations (Phase 3 studies OB-301, OB-301 and OB-303, Phase 2 studies OB-201, OB-202, DM-230, DM-231, OB-205, the Phase 1 study OB-118, the ISS and ISE, and the Phase 1 study OB-118). The analysis data sets should be developed following conventions for ADaM. Please refer to Appendix Z regarding Analysis Data Model (ADaM).
- It is acceptable to submit Item 11 datasets for studies OB-102, OB-103, OB-105, OB-106, OB-107 and OB-108. However, in the event that during the course of the review it becomes necessary to work with analysis datasets from any of the studies with Item 11 datasets, we will contact VIVUS and discuss the best method to obtain the needed information.
- We agree with your plan to submit the SAS programs used to create clinical study report tables and figures for all studies except OB-101.

Clinical Pharmacology:

- Your plan is acceptable.

Meeting Comments

Vivus noted that study OB-201 was conducted by an individual researcher prior to transfer of the IND. Therefore, they cannot produce SDTM formatted data for this trial. The other three phase 2 trials were reported based on Item 11 datasets. Vivus would prefer to submit as Item 11 data rather than as SDTM.

FDA commented that it is preferable to follow a common format and this would be discussed internally.

Vivus pointed out that all the integrated data – including 3 phase 2 studies – were in SDTM format. The only exception was the investigator study (OB-201), which represented a minor contribution (50 subjects).

In addition, the phase 2 data is not in ADaM, however, all phase 3 data were in ADaM and SDTM. The Division noted that, while our preference is for datasets to be submitted in CDISC or the ADaM format for analysis datasets, it is not a requirement at this time.

Clinical Question 5:

Does the Agency agree with VIVUS' plan for identification and assessment of TMEs and related submission of patient profiles?

FDA Response:

We agree with your proposal to assess medical events of interest as 'TMEs' and to submit the patient profiles in these cases. TMEs and patient profiles should be provided for the Phase 2 studies as well as Phase 3. TME analyses should be conducted in the ISS as part of the pooled analyses.

We agree with your rationale to exclude certain terms from the depression and drug abuse SMQs that you will be assessing elsewhere for a more specific presentation of events, but you should also present the data including all those terms within the prespecified SMQs as separate analyses.

For those TMEs that do not utilize standard MedDRA SMQs, please describe your process for selecting MedDRA preferred terms for inclusion or exclusion from a particular TME.

Preferred terms related to cardiac events, in particular those related to ischemia and arrhythmia (see respective MedDRA SMQs), should be included in the list of TMEs. It is unclear why 'menstrual disorders' is included as a TME.

Meeting Comment: No further discussion

Clinical Question 6:

Does the Agency accept that CRFs cannot be submitted for any OB-201 patients and agree that CRFs will not be required for any patients enrolled in this study?

FDA Response:

Please clarify the status of the source documents and why they have not been made available to VIVUS. Is VIVUS confident that proper data management procedures were followed with the conversion of the data to Excel? Are there data from the source documents that were not made available to VIVUS?

We remind you that financial disclosure information is required for OB-201.

Meeting Comment: No further discussion

Clinical Question 7:

Does the Agency agree that individual patient DEXA analysis variable data will be submitted as part of the data listing, but that original DEXA images will not be submitted?

FDA Response:

Yes.

Meeting Comment: No further discussion

Clinical Question 8:

Assuming that the review of data does not identify significant, currently unknown risks that would necessitate a more complex or active risk management plan, does the Agency agree with this approach regarding the development of the RMP?

FDA Response:

Before FDAAA, FDA approved certain drug and biological products with risk minimization action plans (RiskMAPs). A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. RiskMAPs were developed to manage risks that require additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required reporting.

Because many of the purposes of a RiskMAP can be met with a Risk Evaluation and Mitigation Strategy (REMS), and REMS are enforceable under FDAAA, products that would have previously been approved with a RiskMAP will, instead, be approved with a REMS.

Because you plan to submit a Medication Guide, we recommend that you submit a proposed REMS with your NDA. At a minimum, the REMS would include a Medication Guide and a Timetable for Submission of Assessments. Whether or not additional REMS elements would be required is a review issue and would be communicated to you during the review cycle.

When submitting a Risk Evaluation and Mitigation Strategy (REMS), please include all planned materials identified within the plan that will be necessary to implement your proposal. Education provided as part of a REMS should emphasize the safety messages important for the safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

Meeting Comments

Vivus requested clarification of expectations regarding a timetable for submission of assessments.

FDA noted that the timetable for submission of postmarketing assessments is published and is expected by 18 months, by 3 yrs and by 7yrs.

FDA agreed to provide the sponsor with a template for the proposed REMS.

Clinical Question 9:

Does the Agency agree with VIVUS' plan to include literature and SBA information on phentermine HCl and topiramate, in addition to the VIVUS-sponsored studies, for the Summary of Clinical Pharmacology (Section 2.7.2)?

FDA Response:

Yes

Meeting Comment: No further discussion

Clinical Question 10:

Does the Agency agree with the Sponsor's plans, as outlined in the draft SAP in Appendix 8, for population PK and PK/PD analyses?

FDA Response:

The Population PK & PK/PD analysis plan appears to be acceptable. We suggest that the model should be able to account for both monotherapy and combination therapy, especially since population PK modeling has been done for each agent when administered alone.

Meeting Comment: No further discussion

Clinical Question 11:

Does the Agency agree with the Sponsor's plan for submission of data components from the population analyses, also described in Appendix 8?

FDA Response:

The plan for data submission appears to be acceptable. We recommend the data used in the PD model have both data after single drug administration and in combination to 1) resolve all model parameters discussed in the PK/PD analysis plan and 2) determine whether a pharmacodynamic interaction is present.

Meeting Comment: No further discussion

Clinical Question 12:

Does the Division agree that scheduling for VI-0521 will be the same as phentermine (Schedule IV)?

FDA Response:

A final recommendation on CSA scheduling of VI-0521 will occur following a thorough review of the abuse-related data submitted in the NDA.

Meeting Comment: No further discussion

Clinical Question 13:

Does the Division agree that the proposed analysis plan will be adequate to meet the requirements for providing abuse, dependence and withdrawal data for the VI-0521 NDA?

FDA Response:

1. The proposed analysis plan is generally well-designed to capture events in clinical studies that reflect abuse-related occurrences.
2. CSS recommends that the Sponsor utilize the following list of standard abuse-related adverse events terms, which are based on our experience to date. The list includes specific terms that are in the MedDRA dictionary and frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes is a key observation that may influence a recommendation for scheduling. However, the overall behavioral profile and pharmacologic similarity to a scheduled drug is critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-Related Terms

* Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high*, high*, high feeling*, laughter (* Terms that clearly are not pertinent or relevant such as “high blood pressure,” “respiratory depression,” etc. should be excluded).

* Elevated mood: mood elevated, elation

* Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey

* Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged

* Feeling of relaxation: Feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness

* Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy

* Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts

* Hallucination: (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted

Terms Related to Impaired Attention, Psychomotor Event, Cognition, and Mood:

* Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor

* Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional lability, emotional

disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability

* Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders

* Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative and Psychotic Terms:

* Psychosis: psychotic episode or disorder

* Aggressive: hostility, anger, paranoia

* Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity

3. CSS reminds the Sponsor that the NDA should contain an abuse potential section that contains the necessary elements for fully assessing the abuse potential of a drug (21 CFR § 314.50 (d) (5) (vii)). The assessment of a drug's abuse potential under an NDA submission includes a proposal for scheduling the drug and all scientific information that forms the basis of the proposal, as described below:

1. Chemistry (including chemical similarity to other drugs of abuse)
2. Pharmacokinetics and pharmacodynamics
3. Abuse potential studies in animals and humans (including studies evaluating physical dependence), if conducted
4. Assessment of adverse events in clinical studies related to abuse potential
5. Information on incidence of misuse, abuse, physical dependence, tolerance, and diversion during clinical studies
6. Integrated summaries of safety and efficacy (ISS and ISE)
7. Information related to overdose
8. Epidemiological information on abuse potential, if available
9. Foreign experience with the drug (including adverse events, abuse potential, marketing and labeling), if available

Meeting Comment: No further discussion

Quality

Quality Question 1:

Does the FDA agree that the two drug loading levels [REDACTED] (b) (4) for PHEN Beads will be acceptable for commercial production, as described?

FDA Response:

Yes, we agree with the [REDACTED] (b) (4)

Meeting Comment: No further discussion

Quality Question 2:

Does the FDA agree that the program described is adequate to qualify Topiramate, USP manufactured with the [REDACTED] (b) (4) procedure for commercial production of PHEN/TPM Capsules?

FDA Response:

Yes, your comparability program is acceptable.

Meeting Comment: No further discussion

Quality Question 3:

Does the FDA agree with VIVUS' plan to [REDACTED] (b) (4)

FDA Response:

No, [REDACTED] (b) (4)

Meeting Comment

FDA requested that all supporting information be submitted to the IND for FDA's review prior to the NDA submission.

[REDACTED] (b) (4)

The sponsor inquired about the feasibility of a waiver for such in vivo bioequivalence study (biowaiver) via the following approaches:

- **Biopharmaceutics Classification System (BCS) Class 1 status**

- **In Vitro In Vivo Correlation (IVIVC)**

The sponsor also inquired whether the Division has any official BCS Class 1 status information for phentermine and topiramate. The Clinical Pharmacology reviewer and Chemistry reviewer confirmed that there is neither information on phentermine nor on topiramate for the official BCS Class status. The Division urged the sponsor to submit the evidence of BCS Class 1 status for phentermine and topiramate as well as the IVIVC related justification so the Division can review and make recommendation accordingly.

Quality Question 4:

Does the Agency find the methods proposed for dose differentiation, including the use of different color combinations to be acceptable?

FDA Response:

Yes, the approach for dose differentiation is acceptable. We remind you to include information to show that the components of colors are in compliance with the food additive regulations.

Meeting Comment: No further discussion

Quality Question 5:

Does the FDA agree that the manufacturing scales for the four dose levels of the PHEN/TPM Capsules for the pivotal Phase III clinical trials batches and registration batches are acceptable to permit the proposed scale of commercial manufacturing batch size summarized in Table 15?

FDA Response:

The scale up [REDACTED] ^{(b) (4)} should be justified by providing supporting information (e.g. dissolution data, content uniformity etc.)

Meeting Comment: No further discussion

Quality Question 6:

Does the FDA find VIVUS' proposal for the extent of the stability data that will be available at the time of submission of the NDA/eCTD acceptable and adequate for NDA review?

FDA Response:

No. You should submit a complete stability package in the original NDA, including at least 12 months of long-term data. While we may attempt to review amendments containing stability updates, the review of such amendments will depend on the timeliness of submission, extent of submitted data, and available resources. Therefore, in accordance with Good Review Management Principles and Practice (GRMP) timelines, we cannot guarantee that we will be able to review such amendments in the review cycle. The shelf life for the product will be based on the long-term and accelerated stability data that is submitted and reviewed.

Meeting Discussion

FDA clarified that the registration batches will be considered the primary stability batches in the NDA for the purpose of determining an expiration dating period for the product. (b) (4)

[REDACTED]

There is no information on the similarity or difference between the packaging components of the commercial product and those of the clinical batches. While each difference can be qualified separately, their combined effect on the stability of the commercial product is unknown. Likewise, even if each difference can be shown to have no impact on effectiveness, the impact on stability is unknown. It was noted that the sponsor indicated in the briefing package that topiramate is an unstable compound.

FDA repeated that the ONDQA management recommends a complete NDA be submitted with 12-month stability data for the primary stability batches and that amendments may or may not be reviewed. However, if the Sponsor chooses to submit less than 12-month data in the NDA, it would not be a Refusal-to-File issue, but it may result in a very short expiry for the product. If necessary, the Sponsor should submit additional data no later than Month 5 of the review cycle.

Quality Question 7:

Will it be acceptable for VIVUS to submit additional stability data on the registration batches during the review period?

FDA Response:

No, see above response to question 6.

Meeting Comment: No further discussion

Quality Question 8:

What is the latest point at which the FDA will find it acceptable for VIVUS to supplement the stability data included in the original NDA/eCTD submission with additional data?

FDA Response:

See above response to question 6.

Meeting Comment: No further discussion

Quality Question 9:

Will the data submitted be considered sufficient to allow printed capsules to be used for the commercial drug product?

FDA Response:

Yes, provided the ink components are in compliance with the food additive regulations.

Meeting Comment: No further discussion

Quality Question 10:

Is the stability protocol design for the registration batches acceptable to the Agency?

FDA Response:

Yes, the stability protocol is acceptable.

Meeting Comment: No further discussion

Appendix A – eCTD Structures

Quality Question 11:

Does the Quality Review Team agree with the proposal for providing the information related to PHEN Beads and TPM Beads as separate PDF reports?

FDA Response:

Yes

Meeting Comment: No further discussion

Quality Question 12:

Would the Quality Review Team prefer one of the suggested locations over the other?

FDA Response:

We have no preference.

Meeting Comment: No further discussion

Quality Question 13:

What is the desired level of bookmarking and hyperlinking if the separate PDF reports are acceptable?

FDA Response:

We have no preference.

Meeting Comment: No further discussion

NonClinical

Nonclinical Question 1:

Are the proposed locations of the literature review reports, and the cross-referencing of those literature reviews from Modules 2 and Module 4 in the NDA\eCTD acceptable?

FDA Response:

Yes. Locating referenced publication in the Literature Review in Module 4 is acceptable.

Meeting Comment: No further discussion

Nonclinical Question 2:

Does the Division have any additional requirements or expectations for the structure, format and content of Module 2.4, 2.6, 2.6.7 and Module 4?

FDA Response:

The Division expects full reports of the nonclinical studies with the NDA submission. The toxicology reports should contain group mean data in a tabulated form with statistical notation in addition to the individual animal data. The histopathology section should describe individual animal findings as well as the tabulated histopathology with incidence and severity scores. Nonclinical studies in real PDF file format rather than scanned images of the data is preferred. The final NDA submission should include a table specifying the drug batches used in non-clinical and clinical studies with links to impurity profiles. The final carcinogenicity study report should include statistical dataset files per guidance" *Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>).

Meeting Comment: No further discussion

Additional Clinical Comments:

- Please note that the ISS and ISE should not only include pooled data, but should be an integrated summary of all the safety and efficacy data available across the development program.
- Key ISS tables (deaths, SAEs, and AEs leading to discontinuation) should hyperlink to the relevant CRFs.

Post-meeting comment: Please provide narratives for deaths and SAEs.

- All pregnancies in the development program should be discussed and their outcomes presented.
- Please explain how RBANS data will be presented in the NDA submission.
- Laboratory (with a particular focus on serum bicarbonate) and vital sign data should not only be presented by mean change but also by shift analyses.

Post-meeting comment: The term “shift analyses” was used incorrectly here – we are mostly interested in laboratory cutoffs of interest (e.g., > 3x ULN, > 10x, ULN, > a critically identified value for a particular analyte, etc).

- In situations where patients were discontinued due to patient request or investigator discretion, any recent adverse events should be described and considered in light of the discontinuation.
- Please describe how post-marketing information for phentermine and topiramate will be included in the NDA.

Post-meeting comment: The Division is in the process of standardizing requests to sponsors at the preNDA stage. Since the July 22, 2009 meeting, some of this information being provided to other companies has become available. We encourage you to consider the following:

1. **The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>. To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template (see Appendix A, below).**
2. **See Appendix B for a standard table to be used for AEs and SAEs.**

Meeting Comments:

Vivus requested clarification regarding the expectations for presentation of post-marketing information.

FDA stated that using TMEs to search AERS data and searching AERS data for phentermine and topiramate coadministration would provide some useful safety information. The sponsor was concerned that post-marketing information would not be relevant to their program, particularly because the doses used were lower than the approved doses of marketed phentermine and topiramate.

DMEP noted that available postmarketing data did have relevance since some patients would take more than the prescribed doses. Postmarketing information would be considered supportive in the NDA.

Post-meeting comments: The Division has determined after internal discussion that post-marketing information can be reviewed by the Agency and that the sponsor does not need to perform a separate AERS review in the NDA. Some strategies for how FDA's search will be conducted are as follows: 1) reported events from cases in which phentermine and topiramate were coadministered will be reviewed, 2) any phentermine searches will exclude cases where there was reported coadministration with fenfluramine, 3) TMEs will be used to target the search, and 4) pregnancy outcomes with topiramate will be investigated.

- Please provide analyses of ALT, AST, total bilirubin, and alkaline phosphatase according to the following cut-points. See the Draft Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation for a full discussion of recommended evaluation of potential DILI in a NDA submission.
 - >3x-, 5x-, 10x-, and 20xULN elevations of AST and ALT.
 - Bilirubin >1.5xULN and >2xULN.
 - ALP >1.5xULN.
 - Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN).

Additional Clinical Pharmacology Comments

- We cannot locate the pharmacokinetic bridging information for the to-be-marketed VI-0521 fixed-dose combination capsule formulation to the marketed product formulations. Is this information included in the background package?
- What formulations did you use in Study OB-103 to assess the food effect and drug-drug interaction (such as VI-0521 fixed-dose combination capsule vs. the coadministration of PHEN 15 capsule and TPM 92 capsule)? Please clarify.
- If the release mechanism of topiramate is due to (b) (4), you should conduct a study to assess the interaction between VI-0521 fixed-dose combination capsule and proton pump inhibitor.
- We recommend you to evaluate the drug-alcohol interaction with your "modified" release product. You should conduct *in vitro* drug release testing initially and may have to follow it up with an *in vivo* study depending on the result of the *in vitro* testing.

Sponsor's Response to the Pre-meeting Additional Clinical Pharmacology Comments (July 21, 2009 e-mail)

Bullet 1: (PK Bridging)

- The PK bridging study comparing VIVUS proprietary modified release (MR) topiramate and immediate release phentermine capsules and marketed topiramate and phentermine tablets was conducted in OB-102. AUC was found to be equivalent for phentermine and topiramate between the VIVUS and marketed products.

Meeting Comments:

Clinical Pharmacology commented on the need to understand the exposure of phentermine and topiramate from the fixed-dose combination capsule (VI-0521) to the exposure of phentermine and topiramate as monotherapy of available commercial products. The sponsor responded that VI-0521 is a stand-alone program and does not refer to any clinical safety and efficacy data from other sponsors' commercial products for phentermine and topiramate. Study OB-301 has 7 treatment arms comparing the monotherapy capsule and the fixed-dose combination capsule at different doses including placebo. The sponsor asserted that Study OB-102 serves as the pharmacokinetic bridge between the fixed-dose combination capsule (VI-0521) and the phentermine and topiramate monotherapy of available commercial products. The sponsor also asserted that they co-administered their phentermine alone beads capsule and topiramate alone beads capsule rather than administering their phentermine and topiramate fixed-dose combination capsule in Study OB-102.

Additionally, Clinical Pharmacology emphasized the need of pharmacokinetic bridge between the sponsor's formulated single arm of phentermine and topiramate that were utilized in Study OB-301 and the commercially available references. Clinical Pharmacology commented that Study OB-301's main objective seems to satisfy the fixed-dose combination rule [postmeeting notes: CFR 21 Part 300.50 (a)] where the fixed dose combination capsule should demonstrate added safety/efficacy benefit beyond that of the single ingredient capsule. In order to accept Study OB-301's results, the single ingredient arm needs to be evaluated against the commercial single ingredient products because the sponsor formulated their single ingredient capsule for Study OB-301. If the sponsor were to formulate their single ingredient capsule that resulted in much too low phentermine or topiramate exposure than that of commercial products, then the added safety/efficacy benefit of the fixed dose combination product over the single ingredient formulations might be overly exaggerated. The sponsor appeared not seeing the need of this pharmacokinetic bridging information because they emphasized again that VI-0521 is a stand-alone program and does not refer to any clinical safety and efficacy data from other sponsors' commercial products for phentermine and topiramate. This discussion ended with Clinical Pharmacology commenting that they will look for this pharmacokinetic bridging information in the sponsor's future NDA submission.

Postmeeting notes: The need of this pharmacokinetic bridging information will be an NDA review issue rather than an NDA filing issue. Clinical Pharmacology will evaluate the use of pharmacokinetic information from the population pharmacokinetic sampling of Study OB-301 for this issue.

Bullet 2: (OB-103)

- OB-103 used the VIVUS proprietary capsule formulation of topiramate and phentermine in the food effect and the single versus combination drug-drug interaction study.

Meeting Comments:

The sponsor clarified that they used the to-be-marketed fixed-dose phentermine plus topiramate combination capsule rather than coadministration of phentermine alone capsule and topiramate alone capsule to conduct Study OB-103. In addition, they used their own phentermine alone capsule and topiramate alone capsule (not commercially available) to conduct Study OB-103.

Bullet 3: [REDACTED] (b) (4)

- VIVUS decided not to evaluate the [REDACTED] (b) (4) formulation of topiramate due to stability issues; therefore, a drug-drug interaction study with a proton pump inhibitor was not necessary.

Meeting Comments:

The sponsor asserted that the mechanism of the “modified” topiramate release from VI-0521 [REDACTED] (b) (4) thus, the sponsor does not intend to conduct a drug-drug interaction study between proton pump inhibitor and VI-0521.

Bullet 4: (Drug-alcohol interaction study with MR topiramate)

- The current topiramate label cautions against the concurrent use of alcohol. In the presence of alcohol VIVUS’ proprietary modified release formulation is not expected to result in peak exposure that exceeds comparable doses of the commercially available immediate release formulation of topiramate.

VIVUS will propose labeling language that is consistent with that of the current topiramate label with respect to the use of alcohol. Does this Division agree?

Meeting Comments:

VIVUS will propose labeling language that is consistent with that of the current topiramate label with respect to the use of alcohol. Does this Division agree?

The Division agrees. The Division also clarified that the recommended alcohol and VI-0521 interaction study was to assess the interaction between alcohol and the “modified” release portion of VI-0521 so as to determine the effect of alcohol on topiramate tmax for efficacy concerns since the purpose for the “modified” topiramate release is to delay topiramate tmax.

The meeting adjourned.

Minutes Preparer: Patricia Madara
Project Manager
Division of Metabolism and Endocrinology Products

Chair Concurrence: Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products

Additional Statistics comments (referenced in responses to Clinical Questions #1, #3 and #4)
APPENDIX Z

CDISC Data Requests to Sponsors
Quantitative Safety and Pharmacoepidemiology Group

Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please provide a Quantitative Safety Analysis Plan (QSAP). The QSAP generally states the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

At a minimum the Safety Analysis Plan should address the following components:

- Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- Safety endpoints for Adverse Events of Special Interest (AESI)
- Definition of Treatment Emergent Adverse Event (TEAE)
- Expert adjudication process (Expert Clinical Committee Charter)
- Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- Analytical methods (e.g., rationale for data pooling or methods for evidence synthesis); statistical principles and sensitivity analyses to be considered.
- When unanticipated safety issues are identified the QSAP may be amended.

Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) should be carefully followed.
 - a. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
 - a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - i. (DV) Protocol deviations
 - ii. (DA) Drug Accountability
 - iii. (PC, PP) Pharmacokinetics
 - iv. (MB, MS) Microbiology
 - v. (CF) Clinical Findings
 - b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
 - i. Tumor information

- ii. Imaging Data
- iii. Complex Inclusion/Exclusion Criteria

3. Variables

- a. All required variables are to be included.
- b. All expected variables should be included in all SDTM datasets.
- c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
- d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
- f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

4. Specific issues of note:

- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
- c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues

- 1. Please specify which ADaM datasets you intend to submit.
- 2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
- 3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.
- 4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
- 5. Please indicate which core variables will be replicated across the different datasets, if any.
- 6. SDTM and ADaM datasets should use the unique subject ID (USUBJID), which should be unique across the submission. The unique subject identifier should be retained across the entire submission.

General Items

- 1. Controlled terminology issues
 - a. Please use a single version of MedDRA for a submission. It does not have to be the most recent version for the ISS.
 - b. We recommend that the WHO drug dictionary be used for concomitant medications.
 - c. Please refer to the CDISC terminology for lab test names.
 - d. Issues regarding ranges for laboratory measurements should be addressed. The sponsor should explain calculations that result in any changes in ranges for laboratory measurements.

APPENDIX A. Recommended Analyses to Address Items in the Clinical Template

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 Exposure-Response Relationships - important exposure-response assessments.
3. Less common adverse events (between 0.1% and 1%).
4. Section 7.4.2 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.4.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.4.2 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.4.3 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.4.3 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.4.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.4.4 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.4.4. – Standard analyses and explorations of ECG data.
12. Section 7.6.4 – Overdose experience.
13. Section 7.5.1 - Explorations for dose dependency for adverse findings.
14. Section 7.5.2 - Explorations for time dependency for adverse findings.
15. Section 7.5.3 - Explorations for drug-demographic interactions.
16. Section 7.5.4 - Explorations for drug-disease interactions.
17. Section 7.5.5 - Explorations for drug-drug interactions.
18. Section 7.5.5 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Regulatory

Regulatory Question 7: (Environmental Analysis)

VIVUS would like clarification from the Division concerning their response. Does the Division want the submission of the calculation prior to the NDA filing?

Quality

Quality Question 3: [REDACTED] (b) (4)

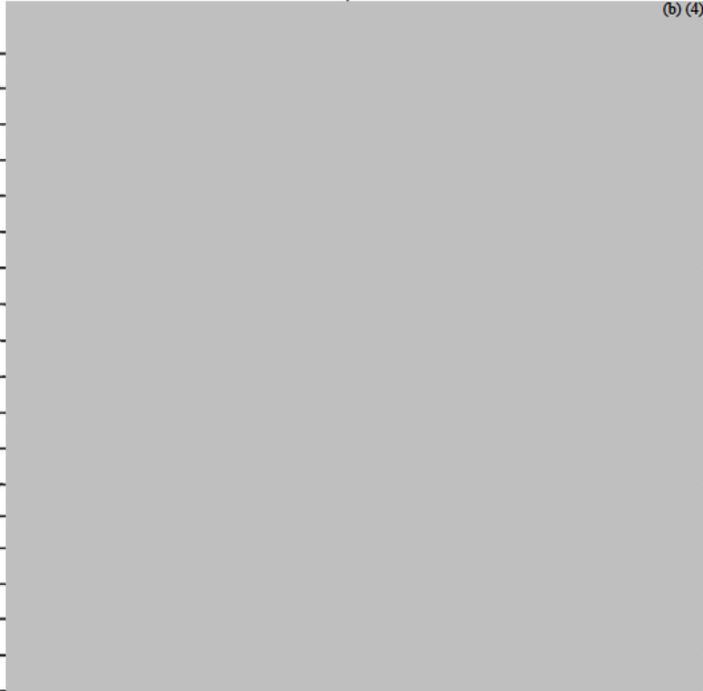
Acknowledged. VIVUS will provide data that demonstrates that [REDACTED] (b) (4) has no effect on bioavailability to include demonstrating pH independent dissolution profile and IVIVC.

Quality Question 6: (Stability)

The attached tables (Reference: Table 1 and Table 2) represent an extension of Table 9 from the pre-NDA briefing document and summarize the stability data VIVUS will have at time of initial NDA submission for both bottles [REDACTED] (b) (4). Our complete stability package will include up to 18 months of real-time stability for the Phase 3 clinical material which is representative of the commercial material. In addition, accelerated stability data (3 months) will be submitted in the initial NDA filing that supports the use of the Phase 3 clinical and registration lots to support expiration dating. VIVUS would like to discuss this strategy with the Division.

To facilitate FDA resource planning, the attached tables (Reference: Table 1 and Table 2) also show what data we would submit no later than 5 months after submission of the NDA. VIVUS would like to discuss how we may facilitate the review and analysis of our stability data submissions by using a preferred format (such as MS Excel or SAS).

Table 1 Availability of Stability Data for Long Term Conditions for Primary Batches of Drug Product Packaged in HDPE Bottles

Batch number	PHEN/ TPM dose level (mg/mg)	PHEN bead target loading (% w/w)	TPM bead target loading (% w/w)	Estimated Longest Stability Time Point at NDA Submission (months)	Estimated Longest Stability Time Point at Submission of 5 Month Post-Filing Supplement (months)
Phase III 0703794	3.75/23 (low dose)		(b) (4)		(b) (4)
Phase III 0705640					
Phase III 0803708					
Registration batch 1					
Registration batch 2					
Registration batch 3					
Phase III 0703795	7.5/46 (1/2 dose)				
Phase III 0705641					
Phase III 0803709					
Registration batch 1					
Registration batch 2					
Registration batch 3					
Phase III 0703834	15/92 (full dose)				
Phase III 0704640					
Phase III 0705639					
Registration batch 1					
Registration batch 2					
Registration batch 3					

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Clinical

Clinical Question 1:

Appendix Z:

Safety Analysis Plan

VIVUS would like additional clarification surrounding the Quantitative Safety Analysis Plan (QSAP). VIVUS submitted separate SAPs for the ISS and the ISE as part of the pre-NDA briefing document (IND 68651; SN 0179).

Does the Division agree that the ISS SAP will cover the components outlined as applicable by the Division in the QSAP?

Does the Division agree that our presentation of TMEs as amended in clinical question 5, adequately addresses adverse events of special interests?

Clinical Questions 3:

SDTM data was developed for studies OB-202, DM-230, and DM-231, for the purpose of integrating Phase 2 data for the ISS only. Item 11 data will be included for the Phase 2 CSRs. Study OB-201 was conducted under an investigator IND with data transcribed directly from source documents to an excel spreadsheet. It is unlikely that we will be able to create conforming SDTM data from this original dataset. Please see the response to Clinical Question 6 for additional comments about the quality of data from this study.

Clinical Question 4:

SDTM data will be provided for OB-202, DM-230, and DM-231 for use in the ISS. These studies were completed and analyzed previously using Item 11 data and analysis programs. Data presented in the CSR and programs used to generate CSR tables were based on available Item 11 analysis data sets. New analysis data sets using ADaM conventions will not be available for the Phase 2 diabetes studies.

Clinical Question 5:

We will not be able to provide assessment of the TMEs as formally defined in our TME plan, or provide patient profiles for those TMEs for Phase 2 study CSRs, since these studies and CSRs are already complete.

All other requests will be incorporated into the Phase 3 or ISS analysis as applicable.

Clinical Question 6: (CRFs OB-201)

The source documents for the OB-201 study were audited by VIVUS and independent (b) (4) (b) (4) clinical research personnel. Data from this study are also available for FDA audit if required. Because of (b) (4) policy for studies of this nature, sponsor personnel were not permitted to copy information or otherwise remove source information from the site. During audits by both Sponsor and (b) (4) personnel, data in source documents were verified against data in the excel files that were derived for this study. We are confident, therefore, that proper data management procedures were followed.

Clinical Question 8: (REMS)

Will the Division please clarify about their expectations regarding a timetable for submission of assessments?

Additional Clinical Comments:

Bullet 4: (RBANS)

RBANS data will be presented as part of the CSR for each of the studies that incorporated these assessments (OB-202, DM-230, and OB-301). These data will also be presented in the ISS, but as separate data from each study rather than integrated RBANS data. Analyses of RBANS data will focus on identifying between treatment differences in full scale index scores, and scores on particular domains within the instrument and on identifying effect sizes for observed changes.

Bullet 7: (Post-Marketing Information for PHEN/TPM)

VIVUS would like clarification regarding expectations for presentation of post-marketing information.

Additional Clinical Pharmacology Comments:

Bullet 1: (PK Bridging)

The PK bridging study comparing VIVUS proprietary modified release (MR) topiramate and immediate release phentermine capsules and marketed topiramate and phentermine tablets was conducted in OB-102. AUC was found to be equivalent for phentermine and topiramate between the VIVUS and marketed products.

Bullet 2: (OB-103)

OB-103 used the VIVUS proprietary capsule formulation of topiramate and phentermine in the food effect and the single versus combination drug-drug interaction study.

Bullet 3: [REDACTED] ^{(b) (4)})

VIVUS decided not to evaluate the [REDACTED] ^{(b) (4)} formulation of topiramate due to stability issues; therefore, a drug-drug interaction study with a proton pump inhibitor was not necessary.

Bullet 4: (Drug-alcohol interaction study with MR topiramate)

The current topiramate label cautions against the concurrent use of alcohol. In the presence of alcohol VIVUS' proprietary modified release formulation is not expected to result in peak exposure that exceeds comparable doses of the commercially available immediate release formulation of topiramate.

VIVUS will propose labeling language that is consistent with that of the current topiramate label with respect to the use of alcohol. Does this Division agree?

WHY the Combination?

Complementary Effects

Topiramate

Weight loss due to increased satiety

Safety:

- Cognitive slowing
- Muted Mood
- Calming
- Sedating
- ↓ Blood pressure

Hypothesis:

Additive Efficacy



Lower Doses

Cancellation of AEs



Improved Tolerability



Effective Therapy

Phentermine

Weight loss due to decreased hunger

Safety:

- ↑ Memory/concentration
- Elevated Mood
- Anxiety/nervousness
- Insomnia
- +/- Blood pressure

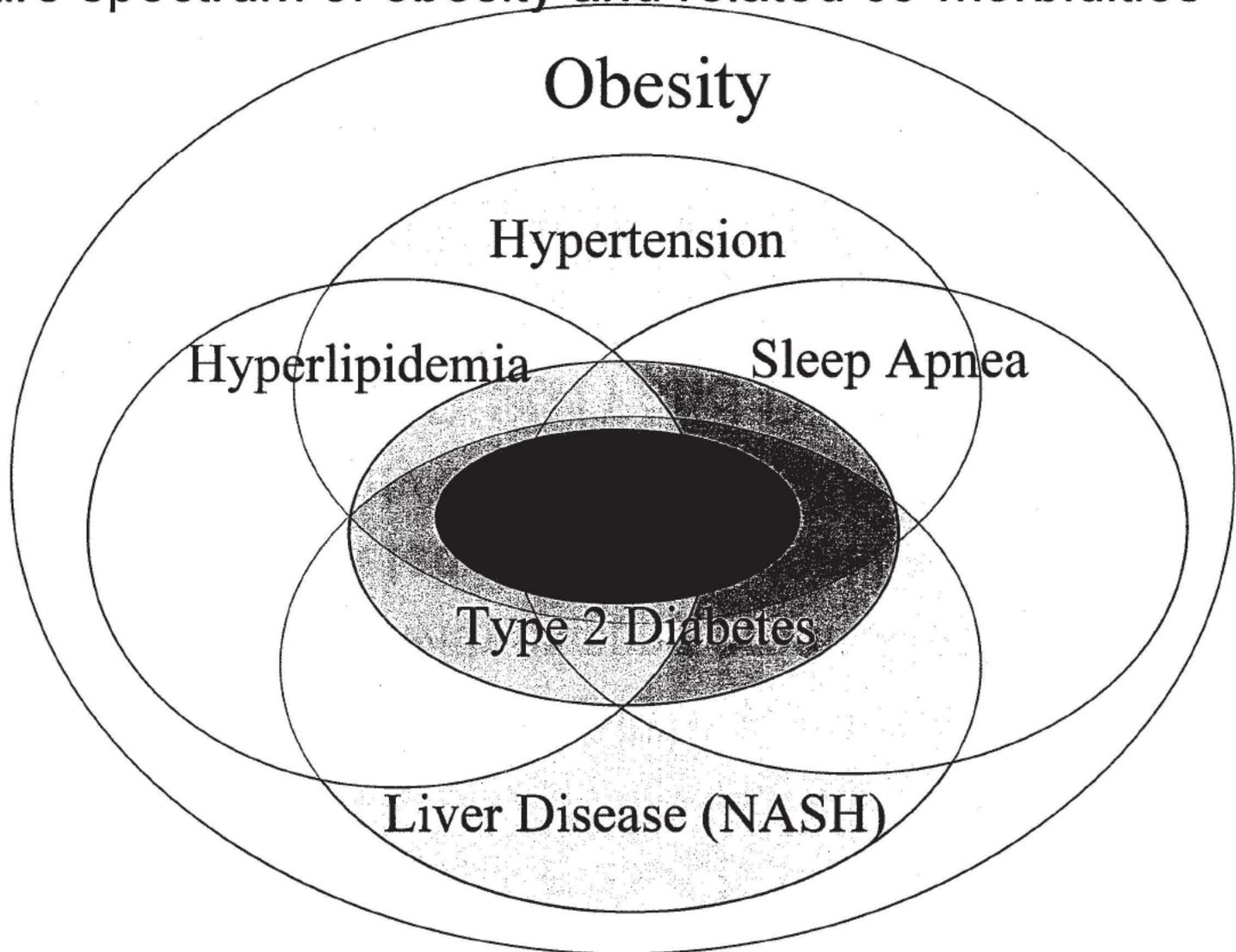
Topiramate is Effective in Obesity and Obesity-Related Comorbidities

Author	N	Population	Duration	Doses (mg)
Bray 2003	385	Healthy Obese	24 weeks	64, 96, 192, 384
Wilding 2004	1289	Healthy Obese	2 years*	96, 192, 256
Tonstad 2005	531	Obese with Hypertension	1-year*	96, 192
Stenlof 2007	541	Obese Diabetics (drug-naïve)	1-year*	96, 192
Rosenstock 2007	111	Obese Diabetics (drug-naïve/Met)	16 weeks	175 controlled release (CR)

* Sponsor ended study early to develop CR formulation

Obesity Syndrome

VI-0521 program designed to demonstrate benefit/risk across entire spectrum of obesity and related co-morbidities



VI-0521: Clinical Program Update

- Clin Pharm program complete (9 studies)
 - Results consistent with existing product labels
 - TQT study completed, no issues identified
 - Psycho-motor study completed, analysis underway
- Phase 2 Obesity (OB-201) and Diabetes (OB-202/DM-230,231)
 - POC/dose confirmation studies complete
- Phase 2 Sleep Apnea
 - POC study fully enrolled
 - Interim analysis complete

Phase 3 Obesity Program

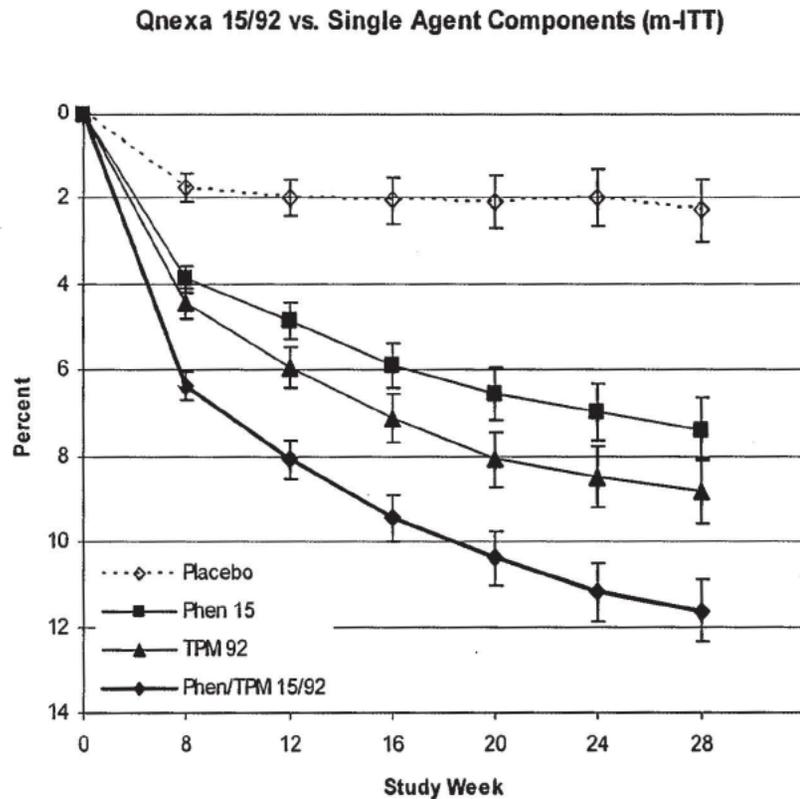
SPA Process Engaged

	Population	BMI	Duration	Dose (92/15mg) (46/7.5mg) (23/3.75mg)	Subjects	Primary Result ITT (LOCF)
EQUATE (OB-301)	Obese	36	28 weeks	Full Mid	756	Weight loss 9.2%, 8.5%
EQUIP (OB-302)	Morbidly Obese	>35	56 weeks	Full Low	1,250	Weight loss 10.9%, 5.1%
CONQUER (OB-303)	Overweight Co-morbidities	27- 45	56 weeks	Full Mid	2,500	Q3 2009

VI-0521: Phase 3 Safety Assessments

- Adverse events, labs, PE results, ECG findings
 - TME Analysis
- Quantitative assessments:
 - Cognitive Function (RBANS) in OB-202/230 and OB-301
 - Depression (PHQ-9) in all studies (all visits)
 - Suicidal ideation and behavior (C-SSRS) in all studies (all visits)

Study OB-301: Percent Weight Loss (Full-Dose)

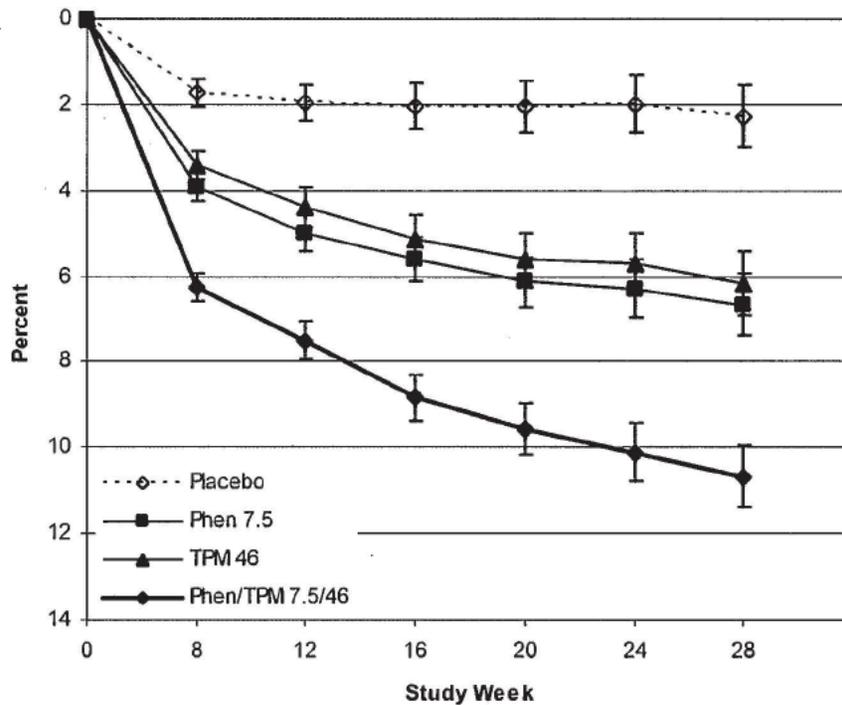


Week 28 ITT-LOCF	
Treatment	Percent
Placebo	1.71
PHEN 15	6.06
TPM 92	6.44
PHEN/TPM 15/92	9.21*

* $p < 0.001$ vs. placebo and single-agent components

Study OB-301: Percent Weight Loss (Mid-Dose)

Qnexa 7.5/46 vs. Single Agent Components (m-ITT)

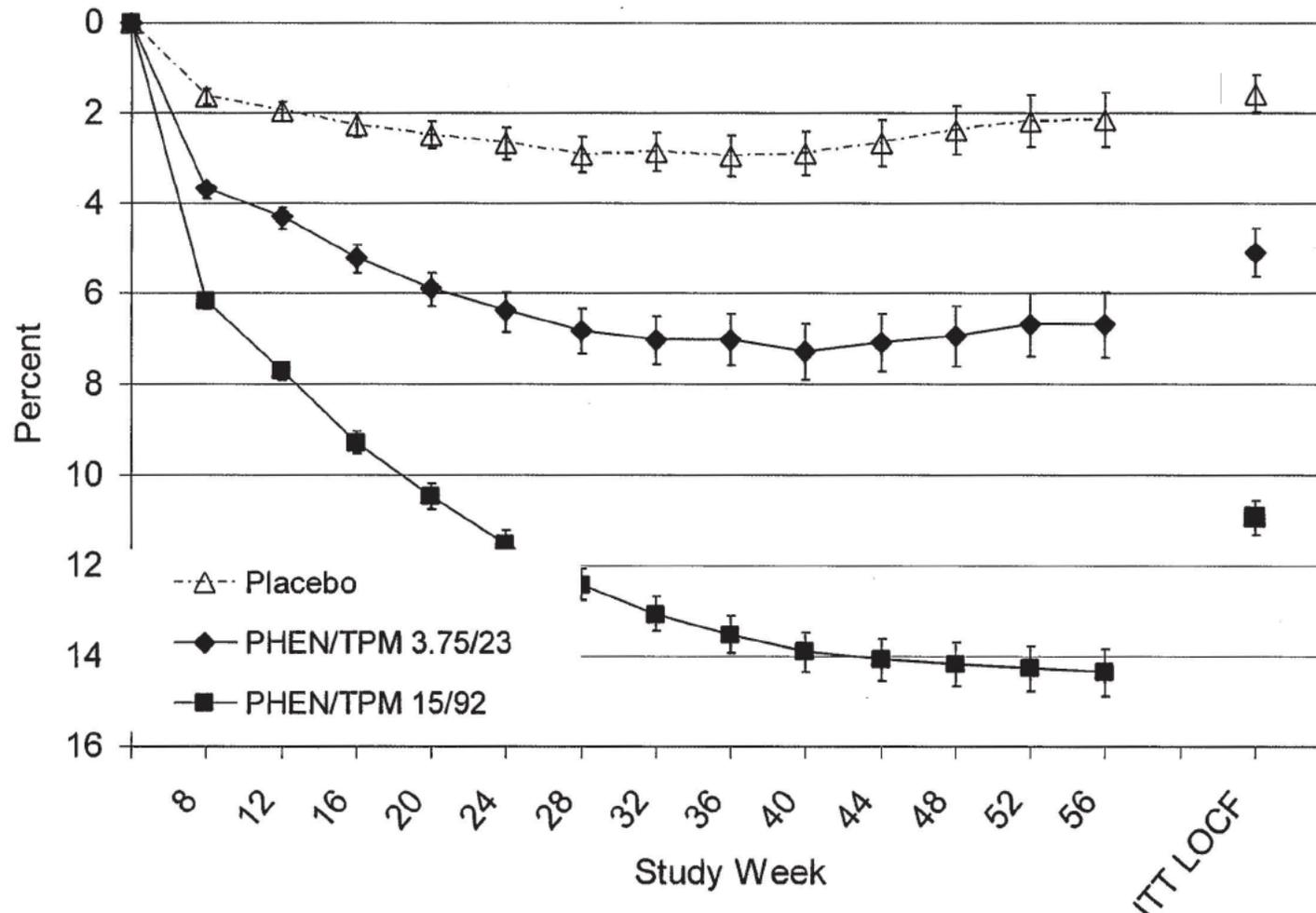


Week 28 ITT-LOCF

Treatment	Percent
Placebo	1.71
PHEN 7.5	5.45
TPM 46	5.13
PHEN/TPM 7.5/46	8.46*

* $p < 0.001$ vs. placebo and single-agent components

UB-302: Percent Weight Loss in Morbid Obese (Low-Dose and Full-Dose)

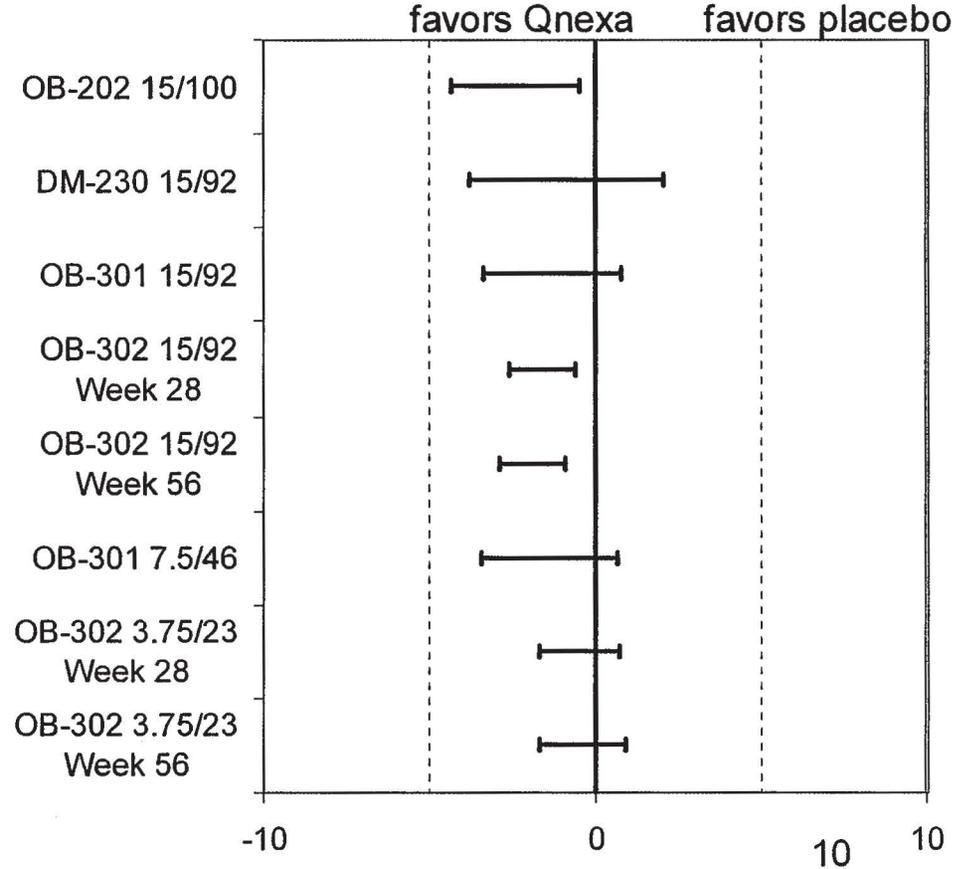
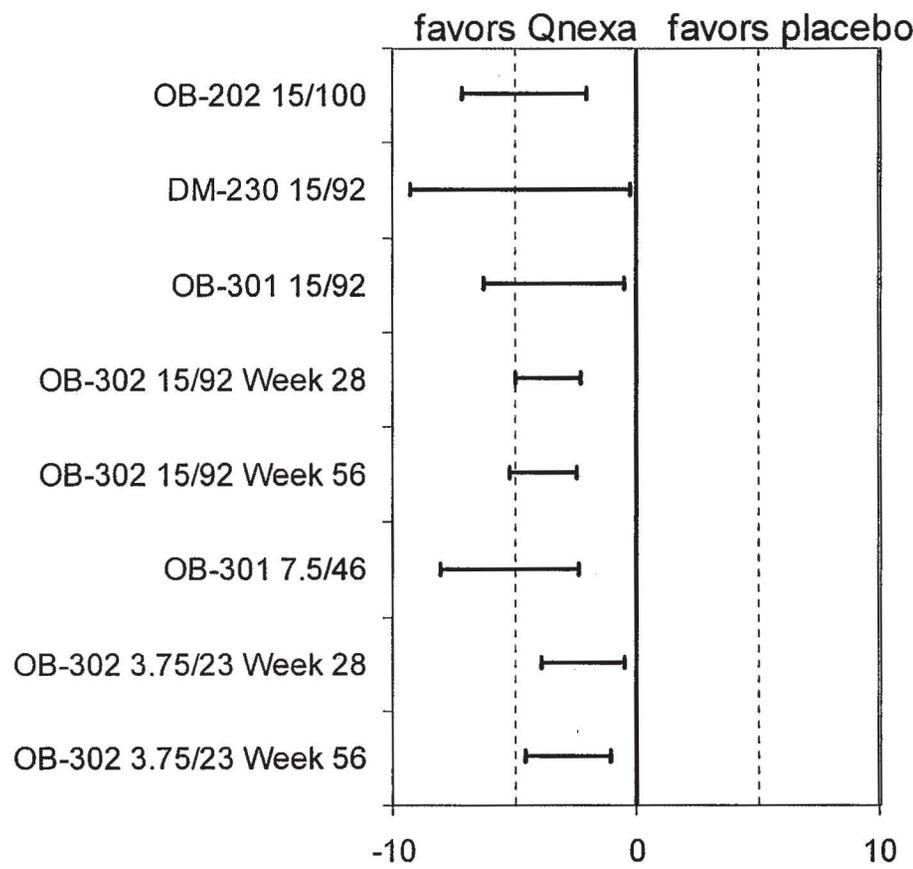


Individual timepoints are observed data from the modified ITT set.
ITT-LOCF also shown for Week 56 data

VI-0521 Program: Effect on Blood Pressure (Low, Mid and Full-Dose)

Placebo-subtracted Change in
Systolic Blood Pressure
(95% CI)

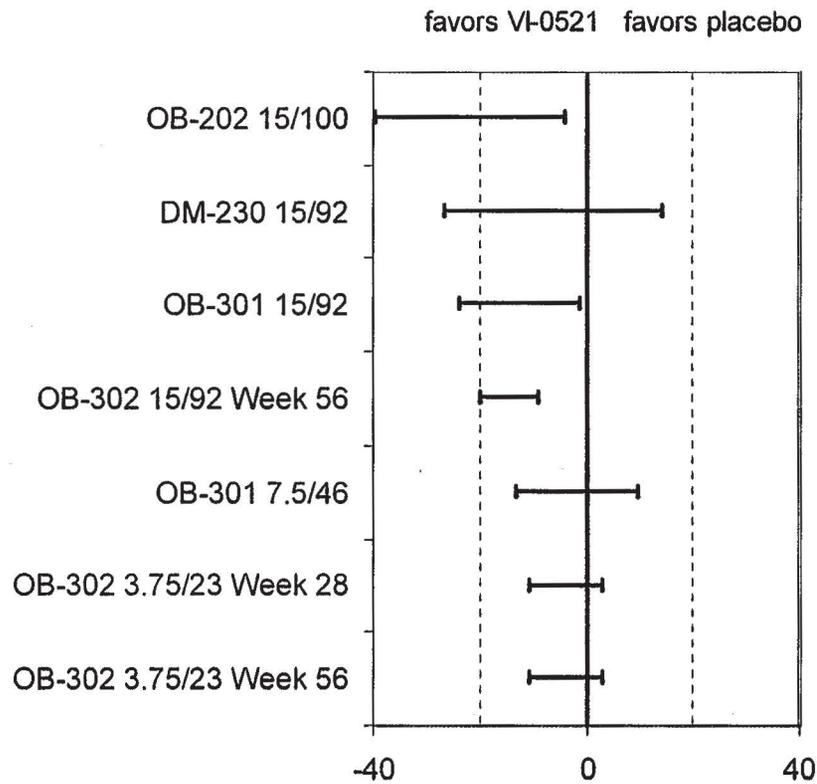
Placebo-subtracted Change in Diastolic
Blood Pressure
(95% CI)



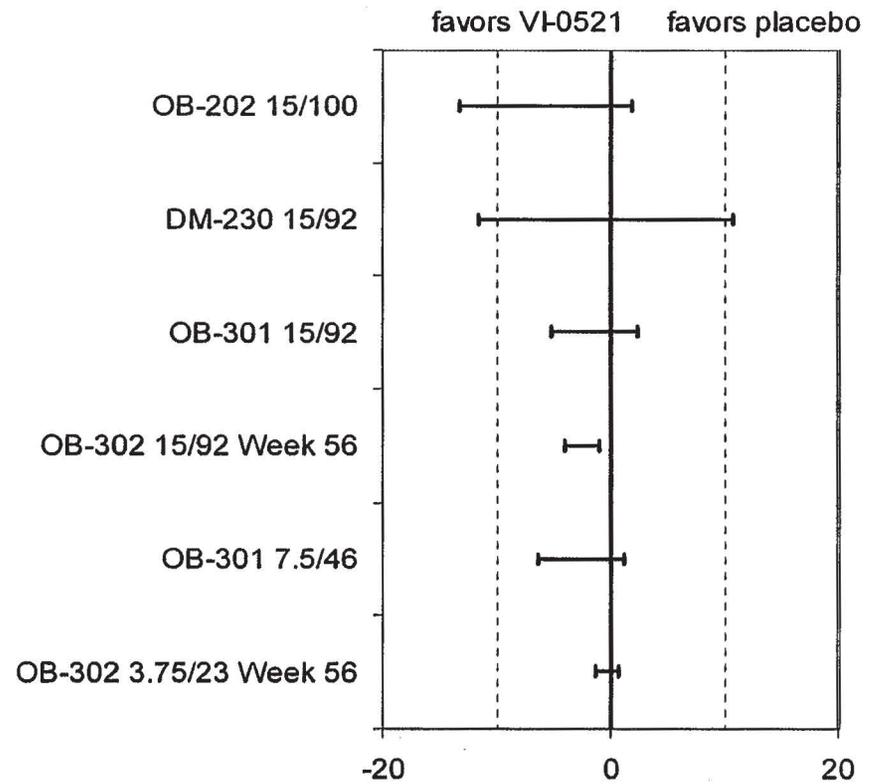
VI-0521 Program: Effect on Lipids

(Low, Mid and Full-Dose)

Placebo-subtracted Change in Triglycerides (95% CI)



Placebo-subtracted Change in Total Cholesterol (95% CI)



Consistent Results Over Multiple Studies

- Dose related effects on weight
- Sustained and progressive efficacy over 1 year for weight loss and HbA1c
- Effective in diabetics and non-diabetics
- Extent of efficacy appears to be related to severity of baseline values

	Pop	N	% Wt Loss*	Waistline (cm)	HbA1c	SBP (mmHg)	TG %	Liver Function (ALT)	QOL	PHQ-9 change
OB-201 6 months	Obese	200	10.7%	-12.1	NA	-6.4	-15	-28%	+	NA
OB-301 6 months	Obese	756	9.2%	-8.7	-0.02%	-5.2 -22.4**	-9	-15%	+	-1.2
OB-302 1 year	Morbid	1200	10.9%	-10.9	NA	-4.0	-6.8	-13.2%	+	-1.5
	Obese		5.1%	-5.6		-4.0	2.8	-8.2%		
OB-202 6 months	DM2	200	8.0%	-6.4	-1.2%	-4.1	-21	-27%	+	-1.4
DM-230 1 year	DM2	130	9.4%	-8.0	-1.6%	-7.2	-21	-15%	+	-1.2

*ITT-LOCF

**Top quartile

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,651

Vivus, Inc.
Attention: Jacqueline A. Dombroski, Ph.D.
Senior Director, Regulatory Affairs
1172 Castro Street
Mountain View, CA 94040

Dear Dr. Dombroski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for phentermine / topiramate fixed dose combination tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 2, 2007. The purpose of the meeting was to discuss specific questions related to your Phase 3 development program.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301)796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 2, 2007
TIME: 11:00 AM
LOCATION: Teleconference
APPLICATION: 68,651
DRUG NAME: phentermine/topiramate fixed dose combination
TYPE OF MEETING: End of Phase 2

MEETING CHAIR: Eric Colman, M.D., Deputy Director

MEETING RECORDER: Patricia Madara

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Pat Madara, M.S.	Regulatory Project Manager

Division of Clinical Pharmacology II

Johnny Lau, Ph.D.	Acting Team Leader
Sally Choe, Ph.D.	Clinical Pharmacology Reviewer

Controlled Substances Staff

Patricia Beaston, M.D., Ph.D.	Medical Officer
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EXTERNAL CONSTITUENT ATTENDEES:

Vivus, Inc.

Wesley Day, Ph.D.	VP, Clinical Development (VIVUS' Meeting Chair)
Jacqueline Dombroski, Ph.D.	Sr. Director, Regulatory Affairs
Craig Peterson	Sr. Director, Clinical Research
Barbara Troupin, M.D.	Director, Clinical Development
Peter Tam, M.B.A.	Sr. VP, Product & Corporate Development
Sandra Hunter	Regulatory Affairs Specialist

BACKGROUND:

IND 68,651 is for a new formulation of phentermine / topiramate (delayed release) in a fixed dose combination. It is being developed as a treatment for obesity. Vivus, Inc submitted a briefing document containing specific questions on March 16, 2007. Draft responses were provided by the Agency on April 26, and 27, May 1 and 2, 2007. Vivus determined that the clinical and preclinical responses were clear and complete, requiring no further discussion. However, it was felt that additional discussion of the clinical pharmacology and abuse liability questions would be beneficial.

The original questions and draft responses are repeated below in regular font. (Only those questions requiring discussion at the meeting are included below.) Additional comments made by the Agency are in **Bold** font and additional remarks by Vivus are in *italics*.

Question #14

Does the Division agree that the proposed cognitive, neurologic, psychiatric, mood and suicidality assessments provide appropriate oversight of these safety concerns in the clinical program?

DMEP Response:

- Yes. Follow-up data should be collected on all patients referred for specific evaluation of cognitive, neurological, or psychiatric adverse events. Note: The Controlled Substance Staff will likely have additional recommendations in response to this question. (The CSS responses will not be available until COB on Tuesday.)

CSS Response:

- Clear documentation of psychological adverse events is important for assessment of abuse liability and related safety evaluations. The clinical protocols and MedDRA coding should include instructions for the collection and documentation of these events.

The cognitive tests proposed appear adequate. However, the protocol should state how these assessments will be performed, including the timing of the testing relative to dosing, and how the data will be analyzed. Evaluation of psychometrics should include psychomotor testing.

Additional CSS comments:

- **Because all of the subjective complaints (verbatim terms) will map to a preferred term (PT) in MedDRA some confusion may arise in the interpretation of these adverse events. Coding conventions help limit this occurrence. We refer you to the document 'MedDRA term selection: Points to Consider'.**

Additional Sponsor questions:

Regarding the last sentence of the CSS response, we had included cognitive testing which included symbol-digit modality testing. However, this does not have a motor function, except for some writing.

Additional CSS comments:

- **There is a spectrum of psychomotor tests, for example, such things as driving a joy stick to follow a path, that measures response time and eye/hand coordination. Discuss the available tests with your consultants. Include the chosen psychomotor tests in the protocols submitted for review by CSS.**

- **Examples of psychometric and cognitive tests include:**
 - **Critical Flicker Fusion (CFF);**
 - **Choice Reaction Time-Hicks (CRT);**
 - **Compensatory Tracking Task (CTT);**
 - **Mental Arithmetic Task (MAT);**
 - **Rapid Visual Information Processing Task (RVIP);**
 - **Sternberg's Short Term Memory Scanning Task (STM);**
 - **Immediate and Delayed Recall of Supraspan Word Lists (WRi and WRd);**
- **The psychomotor testing can be limited to a sub-study in a large phase 3 clinical trial to support safety and labeling. However, if abuse liability studies are proposed then all subjects should undergo testing. Testing in abuse liability assessments must include the:**
 - **Addiction Research Center Inventory (ARCI 49).**
- **Since the phentermine-topiramate combination product is a Schedule IV drug under the Controlled Substances Act, drug accountability and tracking procedures should be established to account for any losses, overuse, or possible diversion.**

Question #16

Does the Division agree that Special Population Studies in renal and hepatic impaired patients and drug Interaction Studies are not necessary?

Clinical Pharmacology Response:

- No. The Agency strongly recommends that you conduct renal impairment, hepatic impairment, and drug interaction studies.

Renal excretion seems to be the major elimination pathway for both topiramate and phentermine. Renally-impaired subjects will have significantly different exposures compared to subjects with normal renal function. The exposure information of both drugs in renally-impaired subjects will help guide appropriate dosing for this population of patients. Also, the exposure information in hepatically-impaired subjects has not been reported for both drugs. The marketed topiramate product labeling mentions that clearance may be decreased in hepatically-impaired subjects. The exposure information of both drugs in hepatically-impaired subjects will help guide dosing in this population of patients.

In addition, the Agency recommended conducting a drug-interaction study with oral contraceptives at the March 16, 2006 Type C teleconference meeting, and this recommendation still stands. We also recommend a drug-interaction study with probenecid, which significantly increased topiramate renal clearance in rats via inhibiting tubular reabsorption (marketed topiramate product labeling).

VIVUS' RESPONSE (prior to the meeting)

VIVUS acknowledges the request for information on the following types of studies:

- Renal impairment

- Hepatic impairment
- Drug interaction studies, including oral contraceptives and probenecid

VIVUS agrees to perform clinical studies in subjects with renal and hepatic impairment with VIVUS' fixed combination product.

VIVUS also agrees to investigate the potential for drug interactions between oral contraceptives and VIVUS' fixed combination product. With respect to probenecid, it is not clear what the basis for this study would be since this interaction would not pose a safety issue. It would be acceptable to VIVUS to acknowledge the possibility of such an interaction in the label.”

Additional Clinical Pharmacology Comment (prior to the meeting):

With respect to the probenecid drug interaction study, we were more concerned about efficacy than safety. The meeting briefing package did not offer clear explanation on the mechanism of coadministered phentermine and topiramate to treat obesity as well as the resultant systemic exposure for phentermine and topiramate upon oral administration as a combination product. Hence, the Agency has difficulty projecting the finding of increased renal excretion of topiramate in rats with probenecid into clinical setting. We encourage you to address this concern either via data or justification for waiving the study.

“If the Clinical Pharmacologist still has concerns that would indicate that other specific drug interaction studies will be required, VIVUS would be interested in receiving feedback either in writing or in the tentative telephone conference on 2 May 2007.

Additional Clinical Pharmacology Comment (prior to the meeting):

- We remind you that you need to conduct a relative bioavailability study comparing each individual component (i.e., topiramate and phentermine) of your combination product to the final formulation of VI-0521.

Additional Sponsor Comment:

Vivus confirmed they would conduct studies in renally and hepatically impaired patients. Also, they provided clarification about their phentermine formulation. (b) (4)

However, all the prior clinical studies have been with the commercially available formulation. They will conduct a bioavailability study before starting clinical trials with the new formulation.

Additional Clinical Pharmacology Comments:

Since Study OB-301 (Phase 3) will use your formulated individual phentermine (IR) and topiramate (DR) products, you will need 2 other treatment arms in the recommended relative bioavailability study that compares each of your formulated individual phentermine (IR) and topiramate (DR) products to the coadministered marketed products.

This design will provide exposure information for each of your formulated individual component products and help relate them to those of the individual component marketed products that have established efficacy and safety data.

Additional Sponsor Comment:

Vivus noted that they would do a brief bridging study to determine if the Vivus formulation was comparable to the marketed product.

Additional Clinical Pharmacology Comments:

Our recommended design is similar to your proposed study, except our design eliminates the inter-study variability for comparison.

The recommended relative bioavailability study can be a single dose crossover study with the following 4 treatment arms:

- **your formulated phentermine + topiramate combination product**
- **marketed individual phentermine (IR) and topiramate (IR) products coadministered together**
- **your formulated individual phentermine (IR) product**
- **your formulated individual topiramate (DR) product**

Multiple-dose PK profile of your combination product can be obtained from a separate multiple dose PK study.

The reviewer asked if the PK results and exposure data of the final combination product would be available before the Phase 3 studies.

The type of formulation (delayed vs. modified release) for the topiramate component in your final combination product is unknown. There may be a need to conduct an interaction study between your formulation and co-administered drugs (such as (b) (4) (b) (4) release formulation vs. proton pump inhibitor). Characterizing the mechanism of drug release from the formulation will aid in determination of the need and design of such an interaction study.

Additional Sponsor Comment:

The sponsor commented that they would do a PK study with the combination product. They would also supply single and multidose PK data for each of their formulations compared to the marketed products.

They commented that the strategy for the delayed release topiramate was to protract the Tmax (3-4 hrs later). At the moment there is no human data available using the Vivus formulations.

Question #17

Will it be necessary to perform an assessment of drug abuse liability in a population of recreational drug abusers?

Controlled Substance Staff Response:

- Phentermine and all products containing phentermine are Schedule IV drugs under the Controlled Substances Act (CSA). The determination of abuse liability is made independently of the dose of phentermine in the product.

Additional CSS Comments:

- **Any changes to the current scheduling of phentermine would require formal abuse liability studies. You can submit your proposals for review by CSS. Justification as to the study population chosen and why animal testing is not needed should be included in the discussion.**
- **Vivus should develop an abuse liability program and submit a protocol for comments before requesting a meeting with CSS. Abuse liability studies usually examine at least one dose higher than the dose proposed for clinical use. Safety data should include data on all exposures (durations and doses) to the topiramate/phentermine combination to support the doses proposed for the abuse liability studies. This safety data must be based on the Company's combination product.**

Additional Sponsor question:

Regarding suicidality, we will include information from all Phase 2 and Phase 3 studies. However, some of our studies will be open-label and the guidances suggest including information from controlled clinical trials only.

Additional DMEP Comment:

- **Include data from controlled studies.**

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this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
5/23/2007 03:55:11 PM