

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200063Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 200063

SUPPL #

HFD #

Trade Name Contrave

Generic Name naltrexone hydrochloride/bupropion hydrochloride Extended Release tablets, 8mg/90mg.

Applicant Name: Orexigen Therapeutics, Inc.

Approval Date, If Known 9/10/14

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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

3 years

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?

N/A

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# 020358 Wellbutrin SR (bupropion HCl) extended release tablets

NDA# 018932 Revia (naltrexone HCl) tablets

NDA#

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:

N/A

(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:

N/A

(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:

NB-301 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Two Doses of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects±

NB-302 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Subjects with Obesity Participating in a Behavior Modification Program

NB-303 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects^

NB-304 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Naltrexone 32 mg Sustained Release (SR)/Bupropion 360 mg Sustained Release (SR) and Placebo in Obese Subjects with Type 2 Diabetes Mellitus

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, #3, #4 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:

N/A

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, #2 YES NO

Investigation #3, #4 YES NO

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

N/A

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"):

NB-301 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Two Doses of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects±

NB-302 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Subjects with Obesity Participating in a Behavior Modification Program

NB-303 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Naltrexone Sustained Release (SR)/Bupropion Sustained Release (SR) and Placebo in Obese Subjects^

NB-304 A Multicenter, Randomized, Doubleblind, Placebo Controlled Study Comparing the Safety and Efficacy of Naltrexone 32 mg Sustained Release (SR)/Bupropion 360 mg Sustained Release (SR) and Placebo in Obese Subjects with Type 2 Diabetes Mellitus

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?

Investigations #1 and #2 !
IND # 68858 YES ! NO
! Explain:

Investigations #3 and #4 !
IND # 68858 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: Patricia Madara
Title: Regulatory Project Manager
Date: 9/8/14

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Director, DMEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
09/10/2014

JEAN-MARC P GUETTIER
09/10/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 200063 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Contrave Established/Proper Name: naltrexone HCl 8 mg and bupropion HCl 90 mg Dosage Form: oral tablet		Applicant: Orexigen Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Patricia Madara		Division: DMEP
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:	
Note: 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.		
❖ Actions		
- Proposed action - User Fee Goal Date is 9/11/14	☒ AP ☐ TA ☐ CR	
Previous actions <i>(specify type and date for each action taken)</i>	☐ None CR 1/31/11	
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received	
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 4
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other IA
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

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>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP 9/10/14; CR 1/31/11
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included – see label attached to approval letter
• Original applicant-proposed labeling	☒ Included (2 nd cycle) 2/7/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included – see label attached to approval letter
• Original applicant-proposed labeling	☒ Included 2/7/14
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	☒ Included - see label attached to approval letter
❖ Proprietary Name	Letters: 4/3/14; 8/4/10 Reviews: 4/1/14; 8/2/10
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☐ None 6/10/10 DMEPA: ☐ None 6/4/14+3/11/14+12/7/10 DMPP/PLT: ☐ None , 5/14/14 OPDP: ☐ None 8/29/14+5/14/14+2/1/11 SEALD: ☐ None 12/14/10 CSS: ☐ None 4/16/13 Other: ☐ see risk management section
Administrative / Regulatory Documents	
❖ Administrative Reviews <i>(e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review)</i>	6/10/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	☐ Not a (b)(2) 1/4/11 and 5/15/14
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Included 9/10/14
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

• This application is on the AIP ○ 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>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>4/30/14</u> If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	included
❖ Minutes of Meetings • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	☐ N/A or no mtg 5/26/11 ☒ No mtg cancelled ☐ No mtg 10/1/07 ☒ N/A ☒ N/A
❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	☐ No AC meeting 12/7/10
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 1/31/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 9/10/14; 1/31/11 (CDTL=deputy division director)
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 9/10/14
Clinical	
❖ Clinical Reviews • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ No separate review 8/22/14, 1/31/11, 12/6/10, 5/24/10 ☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical review, 8/22/14; pg 36
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None 1/14/11 (SEALD), 10/1/10 (DCRP),
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☐ N/A 4/16/13, 1/14/11

• Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • 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>)	NN 1/26/11 ☐ None 5/15/14(DPV), 5/5/14 (DRISK); 12/21/10 (DRISK); 12/15/10 (DPV), 8/19/10 (drug util); 8/17/10 (DPV)
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested 5/15/14, 6/15/11, 12/6/10
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review 9/8/14
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None 5/14/14, 5/12/14, 1/4/11, 12/15/10; 5/11/10
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None 5/23/14; 12/23/10; 8/3/10
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ No separate review 12/20/10
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 5/21/14; 12/20/10; 5/26/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested

Product Quality		☐ None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		☒ No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		☐ No separate review 1/4/11
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		☐ None 6/2/14, 5/5/14; 21/21/11; 12/17/10; 10/29/10; 5/28/10
❖ Microbiology Reviews		
☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		☒ Not needed
☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
		☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)		
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		Review dated 10/17/10; page 139
☐ Review & FONSI <i>(indicate date of review)</i>		
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 5/29/14 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		
		☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

⁵ 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.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

From: Madara, Patricia
To: "Teri Johnson"
Subject: RE: NDA 200063 (Contrave) Medguide revisions / other labeling
Date: Thursday, September 04, 2014 12:41:00 PM
Attachments: [FDA to Orex 4Sept14 PI Response to FDA 26Aug2014.docx](#)
Importance: High

Hi Teri;

Yes, I received the MedGuide and I believe we have reached agreement on the content.

Regarding the PI. Please review the attached version which contains some edits and comments. The rationale for our changes comes from upper management and is explained below:

During the August 21 teleconference, the Agency made the suggestion that a descriptive statement would be considered in the text of Section 14 to describe the change in weight among Contrave-treated patients who tolerated the drug for at least four weeks. In your revised label, you populated such a sentence with results from the (b) (4)

We have had further internal discussion, involving both Office of New Drugs and Office of Biostatistics senior management, regarding the most appropriate analyses to include in Contrave labeling with respect to changes in weight. We continue to believe, strongly, that the ITT analyses are most appropriate and that the (b) (4) cannot be interpreted in the manner that you suggest. Furthermore, as we discussed other labeling possibilities (including a "descriptive" sentence such as the one proposed earlier), it was felt that presenting (b) (4) would be misleading. Although perhaps a valid description from a statistical point of view, clinicians – for whom the label is written – (b) (4)

Thus, there is concurrence within OND and OB that this type of statement is not appropriate for labeling.

You have suggested that the (b) (4)

We disagree. One way of determining such a treatment effect would be to conduct a trial using an enrichment design that eliminates patients who do not tolerate the drug during a run-in period before randomization; this was not done in any of your trials. Especially given the differential early discontinuation of study drug between the Contrave and placebo arms, we do not believe that the (b) (4) yields meaningful estimates and, therefore, will not be included in labeling.

Please let me know if you have any questions.

Sincerely;
Patricia 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: Teri Johnson [mailto:tjohnson@orexigen.com]
Sent: Thursday, September 04, 2014 12:12 PM
To: Madara, Patricia
Subject: FW: NDA 200063 (Contrave) Medguide revisions / other labeling

Hi Pat –

I just wanted to make sure you'd received this and also see if you might be able to tell me when we could expect feedback on the proposed PI.

Thanks,
Teri

From: Teri Johnson
Sent: Wednesday, September 03, 2014 10:18 AM
To: 'Madara, Patricia'
Subject: RE: NDA 200063 (Contrave) Medguide revisions / other labeling

Hi Pat –

All of the proposed revisions have been accepted. Please find attached a clean version of the Med Guide.

Best,
Teri

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Friday, August 29, 2014 2:52 PM
To: Teri Johnson
Subject: NDA 200063 (Contrave) Medguide revisions / other labeling
Importance: High

Hi Teri;

Regarding some of the outstanding labeling issues:

1. The patient labeling team and Medication Errors division in OSE made some

revisions to your verbiage in the med guide. They added some things to align with other med guides.

2. The 70-count container and carton labels are acceptable with the dose escalation chart.

Please confirm receipt. Have a good weekend.

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

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/s/

PATRICIA J MADARA
09/04/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) - CVOT PMR revisions requested
Date: Friday, August 29, 2014 4:42:00 PM
Attachments: [2014_8_29_FDA_Response_to_PMR_CVOT_FINAL.doc](#)
Importance: High

NDA 200063

ADVICE / INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion). In addition, reference is made to your resubmission dated December 10, 2013.

Finally, we refer to your email dated August 28, 2014, containing revisions to the FDA proposed CVOT PMR and providing proposed milestone dates. Our comments and revisions are included in the attached WORD document.

We request a response by September 2, 2014.

Thanks for your help. **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

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA J MADARA
08/29/2014



NDA 200063

GENERAL ADVICE

Orexigen Therapeutics, Inc.
Attention: Thomas Bicsak, Ph.D.
Vice President, Regulatory Affairs
3344 N. Torrey Pines Court, Suite 200
La Jolla, CA 92037

Dear Dr. Bicsak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (8 mg naltrexone HCl / 90 mg bupropion HCl) extended release tablets.

In addition, we reference your submission dated December 10, 2013, containing a complete, class 2 response to our January 31, 2011, action letter.

While review of your application is ongoing, this letter communicates a path forward to exclude the possibility that Contrave is associated with an unacceptable level of cardiovascular risk in the post-marketing setting.

The Agency has reached the conclusion that the LIGHT trial, even with the possible inclusion of a second cohort of subjects to allow accrual of more 'on-treatment' major adverse cardiac events (MACE), cannot serve as the primary basis to exclude the possibility that use of Contrave increases the risk for MACE by 40% or more. The extent of unblinding within and outside Orexigen far exceeded the intent of the original Data Access Plan, raising significant concerns about more widespread dissemination of the interim data and its potential impact on the reliability of any data collected from the time of dissemination onward. We are not confident that we would ultimately be able to detect or exclude the possibility that these activities may have biased the trial's results or otherwise compromised its integrity and have concluded, therefore, that the LIGHT trial will not satisfy a post-marketing requirement (PMR) related to cardiovascular safety.

A new cardiovascular outcome trial (CVOT) will be required to exclude a 40% increased risk for MACE among overweight and obese subjects. This should be a multicenter, randomized, double-blind, placebo-controlled trial whose primary objective is to assess the effect of Contrave on the risk of MACE among obese and overweight subjects at high risk of CV events. The primary endpoint of this trial should be a composite of CV death, non-fatal myocardial infarction, and non-fatal stroke (i.e., MACE). The trial should be designed to exclude an upper bound of the 95% confidence interval for the estimated risk ratio (Contrave to placebo) for MACE of less than 1.4. The trial should also be designed to provide sufficient data to reflect the

‘on-treatment’ CV-risk associated with Contrave. Further, the sample size calculation for the trial should take into account that ‘on-study’ events would be censored 365 days after treatment discontinuation. A performance standards document should be submitted along with the final protocol. This document should define trial performance metrics assessed by a trial management team on a regular basis to evaluate the overall performance of the trial with the goal of ensuring its completion in a timely fashion and the generation of sufficiently rigorous data.

Despite our conclusion that LIGHT will not be sufficient to serve as the primary basis to exclude a hazard ratio of 1.4 for MACE, we strongly encourage you to continue the LIGHT trial. The Agency does believe that the LIGHT trial may provide supportive (i.e., not primary) evidence when the effects of Contrave on cardiovascular outcomes are ultimately reviewed. For example, if a different trial design is selected for the second CVOT (e.g., one that omits or revises weight loss or blood pressure thresholds mandating discontinuation of study drug), the final results from the LIGHT trial might provide complementary support. In addition, it is plausible that scientific questions may arise during the review of either of these CVOTs for which the availability of data from a second trial, despite potential limitations, may be beneficial to best characterize the effects of Contrave.

Because we will not rely on the LIGHT trial for the purposes of the PMR related to cardiovascular safety, whether to add a second cohort to the LIGHT trial is beyond the scope of this discussion. Should you agree with us that the LIGHT trial should be continued, we encourage you to continue discussions with your Data Monitoring Committee and Steering Committee to optimize the possibility that the trial will provide useful, interpretable data at its conclusion.

In summary, we propose the following PMR for a new cardiovascular outcomes trial:

- A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with Contrave on the incidence of major adverse cardiovascular events (MACE) in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors. The primary objective of this trial should be to demonstrate that the upper bound of the 2-sided confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Contrave to that observed in the placebo group is less than 1.4. The trial should be designed to provide sufficient data to reflect the “on-treatment” cardiovascular risk associated with Contrave. Sample size calculation should take into account that “on-study” events would be censored 365 days after treatment discontinuation. The ongoing LIGHT trial will not be sufficient to meet this requirement; a new trial is required.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

Please submit by email a copy of the PMR trial description to us with milestone dates, which include Final Protocol Submission, Study Completion, and Final Report Submission.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.

If you have any questions, contact Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, 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/

JEAN-MARC P GUETTIER
08/20/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 PMRs and PMCs - FDA revisions
Date: Wednesday, August 06, 2014 12:42:00 PM
Attachments: [FDA to Orexigen 6Aug14 PMRs and PMCs Response to Sponsor's July 18 version.docx](#)
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion). In addition, reference is made to your resubmission dated December 10, 2013.

We have reviewed your proposed milestone dates for PMRs and PMCs, submitted by email on July 18, 2014, and have requests for revision. (See the attached WORD document.)

Please submit your preliminary responses by email. We request a response by COB (eastern time) on August 13, 2014.

Thanks for your help. **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

PMR/PMC list for NDA 200063
CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest. Internal discussion on a PMR to evaluate cardiovascular outcomes is ongoing.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission**, **Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1. A juvenile animal study with the combination of bupropion and naltrexone to assess post-natal growth and development with additional assessment of behavior, learning and memory.

Final Protocol Submission: July 2015
Study Completion: December 2016
Final Report Submission: March 2017

(b) (4)

A clinical pharmacology (Part A) followed by a 52-week randomized, double-blind and placebo-controlled pediatric study (Part B) under PREA to evaluate the pharmacokinetics, safety, and efficacy of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 12-17 years (inclusive). Part B should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.

(b) (4)

Final Protocol Submission: December 2015

(b) (4)

(b) (4)

(b) (4)

Study (b) (4) Completion (b) (4) May 2020

Final Report Submission: November 2020

3.

(b) (4)

A clinical pharmacology (Part A) followed by a 52-week randomized, double-blind and placebo-controlled pediatric study (Part B) under PREA to evaluate the pharmacokinetics, safety, and efficacy of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 7-11 years (inclusive). (b) (4)
Part B should ~~not~~ be initiated until the results of the adolescent pharmacokinetics, safety, and efficacy trial have been submitted to and reviewed by the Agency.

(b) (4)

(b) (4)

Final Report Submission: (b) (4) June 2024

4. A Thorough QT study designed to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

Final Protocol Submission: Sept 2015

Study (b) (4) Completion (b) (4) June 2016

Final Report Submission: Mar 2017

Postmarketing Commitments

5. Conduct a single-dose pharmacokinetic study in subjects with mild, moderate, and severe hepatic impairment. Include overweight and obese subjects in the study population.

Final Protocol Submission: Sep 2015

Study Completion (b) (4) Nov 2017

Final Report Submission: Aug 2018

6. Conduct a single-dose pharmacokinetic study in subjects with mild, moderate, and severe renal impairment. Include overweight and obese subjects in the study population.

Final Protocol Submission: Sep 2015

Study Completion (b) (4) Nov 2016

Final Report Submission: Aug 2017

7. Conduct a drug-drug interaction study with organic cation transporter 2 (OCT2) substrate, such as metformin, to evaluate the *in vivo* potential of Contrave constituents (bupropion and naltrexone) to inhibit OCT2. The study should test the single-dose pharmacokinetics of the organic cation transporter 2 (OCT2) substrate with and without co-administration of Contrave (preferably at steady-state after multiple doses).

Final Protocol Submission: Sep 2015

Study Completion (b) (4) Apr 2016

Final Report Submission: Jan 2017

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/s/

PATRICIA J MADARA
08/08/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) carton and container labels
Date: Thursday, July 24, 2014 10:43:00 AM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to the following emails from you:

1. July 14th, containing revised container and carton labels for the 70-count bottles
2. July 18th, containing revisions to the 120-count bottle labels (both round and square bottles)
3. July 22nd, containing an explanation that the 70-count bottle would not be initially marketed.

We have reviewed your emails and your revised labels and have the following comments and requests for changes.

1. **Given that the 70-count containers will not be marketed immediately, their description** [REDACTED] (b) (4)
2. **For the 120-count labels, incorporate the following revisions for improved clarity:**
 - a. **On the right side panel of the label, remove the title** [REDACTED] (b) (4) **and the dose escalation table. For patients no longer in the dose escalation stage of therapy, such** [REDACTED] (b) (4) **may be misleading and create patient confusion, leading to dosing errors.**
 - b. **On the right side panel of the label, revise the following statement,** [REDACTED] (b) (4) **to as follows:**
[REDACTED] (b) (4)

Thanks for your help. **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

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PATRICIA J MADARA
07/24/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) PMRs and PMCs
Date: Tuesday, July 15, 2014 10:54:00 AM
Attachments: [2014_7_14Contrave_PMrs_and_PMCs_FDA_Response_to_June_3_version.docx](#)
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion). In addition, reference is made to your resubmission dated December 10, 2013.

We have reviewed your proposed milestone dates for PMRs and PMCs, submitted by email on June 3, 2014, and have requests for revision. (See the attached WORD document.)

Please submit your preliminary responses by email. We request a response by COB (eastern time) on July 21, 2014.

Thanks for your help. **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

PMR/PMC list for NDA 200063
CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest. Internal discussion on a PMR to evaluate cardiovascular outcomes is ongoing.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission**, **Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1. A juvenile animal study with the combination of bupropion and naltrexone to assess post-natal growth and development with additional assessment of behavior, learning and memory.

Final Protocol Submission: Jul 2015
Study Completion: Dec 2016
Final Report Submission: (b) (4) March 2017

2. A clinical pharmacology (Part A) followed by a 52-week randomized, double-blind and placebo-controlled pediatric study (Part B) under PREA to evaluate the pharmacokinetics, safety, and efficacy; (b) (4) of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 12-17 years (inclusive). (b) (4) Part B should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.

Final Protocol Submission: (b) (4)
Trial Completion (b) (4)
Final Report Submission: (b) (4)

3. A clinical pharmacology (Part A) followed by a 52-week randomized, double-blind and placebo-controlled pediatric study (Part B) under PREA to evaluate the pharmacokinetics, safety, and efficacy; (b) (4) of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 7-11 years

(inclusive). **Part B** (b) (4) should not be initiated until the results of the adolescent pharmacokinetics, safety, and efficacy trial have been submitted to and reviewed by the Agency.

Final Protocol Submission: (b) (4)
Study Completion: (b) (4)
Final Report Submission: (b) (4)

4. A Thorough QT study designed to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

Final Protocol Submission: (b) (4) -September 2015
Trial Completion: June 2016
Final Report Submission: Mar 2017

Postmarketing Commitments

5. Conduct a single-dose pharmacokinetic study in subjects with mild, moderate, and severe hepatic impairment. Include overweight and obese subjects in the study population.

Final Protocol Submission: (b) (4) -September 2015
Study Completion: Nov 2017
Final Report Submission: Aug 2018

6. Conduct a single-dose pharmacokinetic study in subjects with mild, moderate, and severe renal impairment. Include overweight and obese subjects in the study population.

Final Protocol Submission (b) (4) -September 2015
Study Completion: Nov 2016
Final Report Submission: Aug 2017

7. Conduct a drug-drug interaction study with organic cation transporter 2 (OCT2) substrate, such as metformin, to evaluate the *in vivo* potential of Contrave constituents (bupropion and naltrexone) to inhibit OCT2. The study should test the single-dose pharmacokinetics of the organic cation transporter 2 (OCT2) substrate with and without co-administration of Contrave (preferably at steady-state after multiple doses).

Final Protocol Submission (b) (4) -September 2015
Study Completion: Apr 2016
Final Report Submission: Jan 2017

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/s/

PATRICIA J MADARA
07/15/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Request for Information
Date: Thursday, June 19, 2014 5:09:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have the following additional comments and requests for information:

- **Contrave given concomitantly with metoprolol can lead to a 4-fold increase in AUC and a 2-fold increase in Cmax for metoprolol. This drug-drug interaction (DDI) due to CYP2D6 enzyme inhibition by bupropion may also affect propranolol, pindolol and carvedilol.**
- **We note that approximately 20% of subjects in both groups were on metoprolol at screening, 13-14% at Year 1 and 19% at End of Treatment. Approximately 7.6% of placebo and 8.5% of NB32 subjects were on carvedilol at screening, 5.3% of placebo and 5.2% of Contrave at Year 1 and 7.4% of placebo and 8.5% of Contrave subjects at End of Treatment. Approximately 0.6% of placebo and 0.7% of NB32 subjects were on propranolol at screening, 0.5% of placebo and 0.4% of Contrave at Year 1 and 0.6% of placebo and 1.0% of Contrave subjects at End of Treatment. We note that only 1 subject (<0.1%) in both groups was on pindolol at screening, 0% at Year 1 and 0% at End of Treatment.**
- **Given this drug-drug interaction between Contrave and metoprolol, we ask that you submit an analysis exploring possible clinical consequences of increased metoprolol exposure in subjects on NB-32 in NB-CVOT. We believe the analysis should include preferred terms that capture symptoms of increased beta-blocker exposure such as syncope-type terms, dizziness, hypotension, bradycardia and bronchospasm in users and non-users of metoprolol in each treatment arm (on-treatment population). In addition, please analyze changes in heart rate that may inform the clinical relevance of this interaction.**
- **Additional analyses should include subjects taking any of the three beta-blockers (metoprolol, propranolol or carvedilol) using the same preferred terms and changes in heart rate.**

Please provide this information by COB July 10, 2014.

You may submit your response informally, via email but also send it officially to the NDA.

Thanks for your help. **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

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PATRICIA J MADARA
06/19/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (contrave) - Request for Information
Date: Friday, June 13, 2014 9:57:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have additional requests for information:

- 1. For subjects that have discontinued study and are not being followed for MACE, please describe the lag time between a person dying and vital status records being updated.**
- 2. Please provide the Steering Committee and DMC minutes from meetings since December 2013.**
- 3. At the time of submission, [REDACTED] (b) (4) [REDACTED] were omitted from the analysis of all-cause mortality because the deaths had not been adjudicated. Please provide on update on the adjudication results of these deaths.**

You may submit your responses informally, via email but also send them officially to the NDA.

We request a prompt response in order to continue our evaluation of your NDA.

Thanks for your help. **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

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/s/

PATRICIA J MADARA
06/13/2014



NDA 200063

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Orexigen Therapeutics, Inc.
Attention: Thomas Bicsak, Ph.D.
Vice President, Regulatory Affairs
3344 N. Torrey Pines Court, Suite 200
La Jolla, CA 92037

Dear Dr. Bicsak:

Please refer to your New Drug Application (NDA) dated and received March 31, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Contrave (naltrexone hydrochloride/bupropion hydrochloride) extended release tablets, 8mg/90mg.

In addition, we reference your December 10, 2013, submission, received on December 11, 2013, which constituted a complete response to our January 31, 2011, action letter.

On May 30, 2014, we received your May 30, 2014, major amendment to this application, in response to our April 11 and May 21, 2014, requests for information. 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 September 11, 2014.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

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
06/10/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 9, 2014

Application Number: NDA 200063

Product Name: Contrave (naltrexone hydrochloride/bupropion hydrochloride) extended release tablets, 8mg/90mg.

Sponsor/Applicant Name: Orexigen Therapeutics

Subject: Requests from FDA related to the CVOT interim analysis and unblinding of data/inform of clock extension

FDA Participants : Eric Colman, M.D. ; Deputy Director, DMEP
Pat Madara, Regulatory Project Manager, DMEP

Sponsor/Applicant Participants : Dawn Viveash, M.D.; Orexigen, Sr. Vice President
Lawrence Roebel; Takeda, Global RA Therapeutic Area Head
Teri Johnson; Sr. Director, Regulatory Affairs

1.0 Background:

NDA 200063, Contrave (naltrexone hydrochloride/bupropion hydrochloride) extended release tablets, 8mg/90mg, indicated for chronic weight management is currently under review in DMEP (second review cycle).

On January 31, 2011, after completion of the first review cycle, a complete response (CR) letter issued. Because mean systolic and diastolic blood pressure and heart rate were statistically significantly higher in the Contrave-treated subjects compared with placebo-treated subjects, the Division had concerns about the cardiovascular safety profile of Contrave when used long-term in a population of overweight and obese subjects. Therefore, it was requested that the company conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile.

After completion of the dispute resolution process, it was determined that Orexigen could resubmit the application and, within two months of the resubmission, provide an analysis of interim data from the CVOT. In order to protect study integrity, the company agreed to firewall the unblinded team, which was to consist of a small, core group of individuals required for data analysis and submission to FDA.

On April 11, 2014, the Division of Biometrics VII requested a list of individuals with access or knowledge of the unblinded data or unblinded analysis results. Orexigen submitted an informal response / listing via email on April 16, 2014. Upon review of this information, OB VII had a subsequent information request sent on May 21, 2014, asking for additional details related to those with "full access," including the date full access was granted and the exact data that were

shared. Orexigen responded informally, via email on May 23, 2014. An official response to both information requests was submitted to the application on May 30, 2014.

DB VII, DMEP and CDER management expressed serious concerns about the wide dissemination of interim data and the ability to maintain the integrity of the study in this situation.

A meeting was held with Orexigen on June 4, 2014, to discuss our significant concerns and the implications that the release of data may have on the approvability of the application (meeting minutes pending). At that meeting, Dr. Jenkins informed the company that more internal discussions would be required. Therefore, the PDUFA goal date of June 11, 2014, would be missed and the approvability of Contrave was not a certainty.

A follow-up, internal meeting was held on June 5, 2014, to determine a path forward. It was determined that the May 30, 2014, submission would be treated as a major amendment, in order to allow for additional internal discussion and review. The new goal date would become September 11, 2014. Also, CDER management requested that more details and clarification about the number of individuals having access to the interim data be provided to the Agency.

Subsequently, DMEP requested a brief teleconference with Orexigen to request additional data and explain the new review timeline.

2.0 Discussion:

Dr. Colman explained that a decision had been made to treat the May 30, 2014, submission as a major amendment, extending the review clock three months. Official notification of this would be sent to the company by midday on June 10, 2014.

In addition, the Division requested clarification on whether individuals who were provided with the results of the LIGHT CVOT interim data still had access to the data and if so what steps had been or will be taken to prevent future access and to destroy any hard copies of the interim data.

Orexigen stated that each situation was different. Individuals outside of the company were often informed verbally or provided with a set of slides. Company employees had the ability to make hard copies of the data.

It was explained that individuals had access to different folders containing data with varying levels of details. Some could print but others only had viewing access. The majority did not have full access to print the clinical study report (CSR). The company indicated they would submit an explanation to the application, containing more details.

Dr. Colman indicated that FDA would be much more comfortable if very few people had access to the data and further access should be blocked whenever possible.

The company indicated they would “turn off” access. In addition, they would attempt to recover and destroy all hard copies of the data. Orexigen stated that external individuals often had no materials to take away from a meeting.

The Division requested that Orexigen submit any data or information that they have gathered which they believe indicate that the interim data have not been leaked to members from the general public.

Orexigen stated they had been monitoring media and investors and there was no evidence that any results had been leaked to the public.

In addition, the company noted that the data had been submitted to the application under review in the European Union (EU). Orexigen had asked the EU to keep these data confidential. They requested that FDA ask the EU also. The Division indicated they had spoken to the EU about this issue.

Dr. Colman noted the Division would continue to hold internal meetings to discuss labeling and PMRs. He stated that a second CVOT and a new cohort in the ongoing CVOT were being discussed. **The Division would try to provide Orexigen with an update on the review by COB Friday June 13, 2014.**

Orexigen commented that they would need to send out a press release, noting that investors and the market would need to be reassured. The company asked about releasing statements related to the Light study. Dr. Colman indicated that any information related to the CVOT should not be included in the press release. **Specifically, he stated that we did not agree with Orexigen including in their planned press release that we have come to agreement with the company on any aspect of the Contrave NDA review – e.g., labeling, PMC/PMRs.**

He stated that in the event that there is further disclosure of the CVOT (LIGHT) interim data, it could jeopardize the approval of Contrave.

The company asked for continuing communication with the Division as the review progressed. Dr. Colman acknowledged that discussions would proceed to the extent possible. He indicated that there may be information to share in approximately two weeks but noted that internal meetings had to occur first and input from senior management would be required.

3.0 Action Items:

Orexigen committed to the following actions:

1. Officially submit to the application a detailed description of the extent to which data was unblinded for each individual and whether they had access to hard copies of the data. They would attempt to retrieve and destroy all hard copies.
2. “Turn off” access to the data for everyone, except a small, essential group of firewalled employees.
3. Officially submit any information indicating or suggesting that the interim data from the ongoing CVOT have not been leaked to the general public.

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/s/

ERIC C COLMAN
06/10/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Request for Information
Date: Wednesday, May 21, 2014 3:20:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have additional requests for information:

- 1. In your April 16, 2014, response to the April 11, 2014, information request you provided a “NB-CVOT Unblinded List.” This listing includes two general categories of the level of access (1) Full Access and (2) Knowledge of Threshold. For individuals identified on this list as having “Full Access”, please provide the following information:**
 - a. The date the individual had “Full Access”**
 - b. A copy of the exact information/data that was shared with each individual. If various forms of information or data were available provide copies of each form of information available to each unblinded individual.**

Please provide this information by COB May 23, 2014.

You may submit your response informally, via email but also send it officially to the NDA.

Thanks for your help. **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

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/s/

PATRICIA J MADARA
06/05/2014



NDA 200063

**ACKNOWLEDGE-
CLASS 2 RESUBMISSION**

Orexigen Therapeutics, Inc.
Attention: Thomas Bicsak, Ph.D.
Vice President, Regulatory Affairs
3344 N. Torrey Pines Court, Suite 200
La Jolla, CA 92037

Dear Dr. Bicsak:

This letter corrects errors in the acknowledgement letter issued on December 20, 2013. Specifically, the receipt date and user fee goal date were incorrect.

We acknowledge receipt on December 11, 2013, of your December 10, 2013, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Contrave (8 mg naltrexone HCl / 90 mg bupropion HCl) extended release tablets.

We consider this a complete, class 2 response to our January 31, 2011, action letter. Therefore, the user fee goal date is June 11, 2014.

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

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/s/

PATRICIA J MADARA
06/02/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Request for information - PMRs / PMCs
Date: Monday, June 02, 2014 4:14:00 PM
Attachments: [2014_6_2_NDA_200063_Contrave_PMRs_and_PMCs.docx](#)
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application. Please find attached a draft list of postmarketing required studies and postmarketing commitments.

We request that you provide milestone dates for each study and return the document to us. **Please respond as soon as possible but no later than Wednesday, June 4th.**

You may submit your responses informally, via email but also send them officially to the NDA.

Thanks for your help. **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

PMR/PMC list for NDA 200063
CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest. Internal discussion on a PMR to evaluate cardiovascular outcomes is ongoing.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1. A juvenile animal study with the combination of bupropion and naltrexone to assess post-natal growth and development with additional assessment of behavior, learning and memory.

Final Protocol Submission:

Study Completion:

Final Report Submission:

2. A randomized, double-blind and placebo-controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 12-17 years (inclusive). (b) (4) should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

3. A randomized, double-blind and placebo-controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of Contrave (naltrexone/bupropion) for the treatment of obesity in pediatric patients ages 7-11 years (inclusive). (b) (4)

should not be initiated until the results of the adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

Final Protocol Submission:

Study Completion:

Final Report Submission:

4. A Thorough QT study designed to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

Final Protocol Submission:

Trial Completion:

Final Report Submission:

Postmarketing Commitments

5. Conduct a single-dose pharmacokinetic [REDACTED] (b) (4)

Final Protocol Submission:

Study Completion:

Final Report Submission:

6. Conduct a single-dose pharmacokinetic [REDACTED] (b) (4)

Final Protocol Submission:

Study Completion:

Final Report Submission:

7. Conduct a drug-drug interaction study with organic cation transporter 2 (OCT2) substrate, such as metformin, to evaluate the *in vivo* potential of Contrave constituents (bupropion and naltrexone) to inhibit OCT2. The [REDACTED] (b) (4) should test the single-dose pharmacokinetics of the organic cation transporter 2 (OCT2) substrate with and without co-administration of Contrave (preferably at steady-state after multiple doses).

Final Protocol Submission:

Study Completion:

Final Report Submission:

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/s/

PATRICIA J MADARA
06/02/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Revisions to containers and cartons.
Date: Wednesday, May 14, 2014 1:32:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have the following requests for revision to the container and cartons:

1. Container label

- a. The established name is ½ the size of the proprietary name, but lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
- b. The left section of the graphic design is larger than the proprietary name, established name, and product strength. Per Guidance: Container Labels and Carton Labeling, April 2013, remove or minimize the graphic design so that it does not compete in prominence with the proprietary name, established name, and product strength.
- c. The product strength is located at the top of the label, separated from the proprietary name and established name. Relocate the product strength so that it is listed below the proprietary name, established name, and dosage form.:
- d. Although the net quantity statement appears away from the product strength, it competes for prominence because of the font size similar to the font size for the strength. Reduce the prominence of the net quantity statement by using smaller font size and consider relocating statement to the top of the label, based on section A.c.
- e. Increase the size and prominence of the warning statement, "Tablets should not be cut, chewed, or crushed" per Guidance: Container Labels and Carton Labeling, April 2013 as this is an important warning statement since manipulating the tablets by cutting, chewing, or crushing can increase the risk of seizures as specified in your package insert labeling.

2. Carton labeling

- a. See sections A.a through A.d.

- b. Orientation of Dose Escalation Instructions table is not oriented in the same direction and placed in the same field of vision as other text on the carton labeling. Relocate the Dose Escalation Instructions table to the back panel of carton labeling to allow for adequate space to orient text in same direction. Information currently located on the back panel can be relocated to panel where Dose Escalation Instructions are currently located.
- c. Images of tablet within the Dose Escalation Instructions table should represent the actual tablet and reflect the true color and imprint. Revise images of tablet per recommendations within Guidance: Container Labels and Carton Labeling, April 2013.
- d. Include the warning statement, "Tablets should not be cut, chewed, or crushed", on the carton labeling per Guidance: Container Labels and Carton Labeling, April 2013.

Please submit draft full-color mock ups unofficially, via email prior to official submission. 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

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/s/

PATRICIA J MADARA
05/15/2014

**PeRC PREA Subcommittee Meeting Minutes
April 30, 2014**

PeRC Members Attending:

Lynne Yao
Rosemary Addy
Jane Inglese
Wiley Chambers
Karen Davis-Bruno (only reviewed Contrave)
Peter Starke
Gregory Reaman
Daiva Shetty
Shrikant Pagay
Barbara Buch
Dianne Murphy

Agenda

NDA	200063	Contrave (naltrexone/bupropion) Partial Waiver_Deferral_Plan	Management of obesity, including weight loss and maintenance of weight loss
NDA	(b) (4)		(b) (4)
NDA	203567	JUBLIA (efinaconazole) Partial Waiver_Deferral_Plan	Topical treatment of onychomycosis

Contrave (naltrexone/bupropion) Partial Waiver Deferral Plan

- NDA 200063 seeks marketing approval for Contrave (naltrexone/bupropion) for the management of obesity, including weight loss and maintenance of weight loss.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA a goal date of June 10, 2014.
- *PeRC Recommendations:*
 - The PeRC agreed with a partial waiver for pediatric patients aged birth to 6 years because studies would be impossible or highly impracticable.
 - The PeRC agreed with a deferral for pediatric patients aged 7 to 17 years because adult studies have been completed and the product is ready for approval.
 - The PeRC agreed that an efficacy study should first be conducted in adolescents, before proceeding with an efficacy study in younger pediatric age groups. The PeRC agreed with incorporating the PK study into the efficacy studies.
 - The PeRC agreed that the juvenile toxicity study should be conducted before the pediatric efficacy studies are conducted.
 - The timeline for pediatric studies will need to be adjusted by the Division after consideration of the appropriate studies to be performed and the sequence in which they should be performed.

(b) (4)

JUBLIA (efinaconazole) Partial Waiver Deferral Plan

- NDA 203567 seeks marketing approval for JUBLIA (efinaconazole) for topical treatment of onychomycosis.

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/s/

JANE E INGLESE
05/12/2014

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness

of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – *A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

Pediatric Population/Patient- *21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

PREA Pediatric Record/Pediatric Page – *The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: 200063

PRODUCT PROPRIETARY NAME: Contrave

ESTABLISHED/GENERIC NAME: naltrexone/bupropion

APPLICANT/SPONSOR: Orexigen Therapeutics, Inc.

PREVIOUSLY APPROVED INDICATION/S:

- (1) _____
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

(1) Contrave®, a dual pro-opiomelanocortin cell [POMC] enhancer, is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification. Contrave is recommended for patients with an initial body mass index $\geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ in the presence of at least one weight-related comorbid condition (e.g., diabetes, dyslipidemia, or hypertension).

BLA/NDA STAMP DATE: 10 Dec 2013

PDUFA GOAL DATE: 10 June 2014

SUPPLEMENT TYPE: NDA Resubmission

SUPPLEMENT NUMBER: 42

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ***active ingredient(s) (includes new combination);*** ***indication(s);*** ***dosage form;*** ***dosing regimen;*** or ***route of administration?***

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ***No***

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ***No***

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ***No***

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***
- Pediatric Record***

1. Pediatric age group(s) to be waived.

- Neonates
- Infants and toddlers (0 to 2 years)
- Children (2 to 6 years)

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.***)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from adult-related conditions on the next page
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the

waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. *(This reason is for Partial Waivers Only)*

3. Provide justification for Waiver:

Sponsor's justification: Obesity in the pediatric population is an increasing concern both in the US and worldwide. As with adults, the mainstay of weight management is lifestyle modification (diet and exercise). Pharmacologic intervention should only be considered after failure of a sufficient attempt at lifestyle modification. Several factors were considered when evaluating whether to study Contrave in the pediatric population, and if so, which segment of the population would be appropriate:

- **Treatment guidelines and recommendations developed by the American Medical Association (AMA), in collaboration with the Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC), position pharmacotherapy for obesity in adolescents (age 12 years and older) as tertiary intervention, behind prevention and various degrees of structured weight management regimens focused on modified eating behavior and increased physical activity.**
- **Although the appropriateness of pharmacologic intervention to treat obesity in children and adolescents is still a subject of debate, weight loss drugs are used in this population, including one [Xenical (orlistat)] that has been approved for use in 12 to 16 year olds.**

Based on these considerations, Orexigen is requesting a partial waiver of the requirement to conduct pediatric studies for Contrave, limiting study to patients 7 to 17 years of age.

The Division believes that a waiver is appropriate for children < 7 years of age. The Division reports that current clinical practice guidelines recommend against pharmacologic therapy for the treatment of pediatric obesity in children < 5 years of age. Weight loss is not recommended in children less than 2 years of age because of the requirement for adequate growth and development and optimal deposition of lipids in the developing nervous system. For patients 2 to 5 years of age, the American Academy of Pediatrics (AAP) recommends weight maintenance through lifestyle modification if the BMI is greater than or equal to the 95th percentile for age and sex.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Sponsor's proposal:

Section 8.4 Pediatric Use

The safety and effectiveness of CONTRAVE in pediatric patients below the age of 18 have not been established and the use of CONTRAVE is not

recommended in pediatric patients.

The Division agrees with the content of this proposed pediatric language, although it may be changed or additional language recommended depending on the results of our label review.

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration	Cancer:
Alzheimer's disease	Basal cell
Amyotrophic lateral sclerosis	Bladder
Atherosclerotic cardiovascular disease	Breast
Benign Prostatic Hyperplasia	Cervical
Chronic Obstructive Pulmonary Disease	Colorectal
Erectile Dysfunction	Endometrial
Infertility	Gastric
Menopausal and perimenopausal disorders	Hairy cell leukemia
Organic amnesic syndrome (not caused by alcohol or other psychoactive substances)	Lung (small & non-small cell)
Osteoarthritis	Multiple myeloma
Parkinson's disease	Oropharynx (squamous cell)
Postmenopausal Osteoporosis	Ovarian (non-germ cell)
Vascular dementia/ Vascular cognitive disorder/impairment	Pancreatic
Actinic Keratosis	Prostate
	Renal cell
	Uterine

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request:

- a. Adolescents ages 12 – 17 years
- b. Children ages 7 – 11 years

2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
See the above rationale for a waiver in children ages 0 to 6 years.

3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)

- a. **Adult studies are completed and ready for approval**
- b. Additional safety or effectiveness data needed (**describe**)
- c. Other (**specify**)

4. Provide projected date for the submission of the pediatric assessment (deferral date): see timeline on next page

DMEP note: Initiation of pediatric studies would occur after completion of our review of the interim safety analysis from the adult cardiovascular outcome trial (CVOT) as well as the juvenile animal toxicity studies. The interim safety analysis from the CVOT should be reviewed by June 2014.

5. Did applicant provide certification of grounds for deferring assessments? Yes No

6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? Yes No
2. Does the division agree with the sponsor's plan? Yes No
We have some recommended modifications, but we do agree with the majority of the sponsor's plan.
3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? Yes No
 - a. Protocol Submission:
 - b. Study Completion:
 - c. Study Submission:

Rat Juvenile Toxicology Study

- (b) (4) Submit final protocol to IND 68,858
- (b) (4) Complete Study
- (b) (4) Submit study report to NDA 200063

Pediatric PK Study #1: Obese Adolescents $\geq 12 \leq 17$ Years of Age

- (b) (4) Submit final protocol to IND 68,858
- (b) (4) Complete study
- (b) (4) Submit study reports to NDA 200063

Pediatric PK Study #2: Obese Pre-Pubertal Children $\geq 7 \leq 11$ years of age

- (b) (4) Submit final protocol to IND 68,858
- (b) (4) Complete Study
- (b) (4) Submit study reports to NDA 200063

Pediatric Efficacy and Safety Study #1: Obese Post-Pubertal Adolescents $\geq 12 \leq 17$ years of age (~300 subjects)

- (b) (4) Submit final protocol to IND 68,858
- (b) (4) Complete Study
- (b) (4) Submit study reports to NDA 200063

Pediatric Efficacy and Safety Study #2: Obese Children $\geq 7 \leq 11$ years of age. The proposed sample size will be provided in the protocol.

- (b) (4) Submit final protocol to IND 68,858
- (b) (4) Complete Study
- (b) (4) Submit study reports to NDA 200063

4. Has a Written Request been issued? Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)

5. Has a PPSR been submitted? Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

1. A Rat Juvenile Toxicology Study to Assess the Effects of Naltrexone and Bupropion (NB) on Post-natal Growth and Development

PT comments from Patricia Brundage:

Nonclinical Studies:

1. Naltrexone, an opioid receptor antagonist, and bupropion, a modulator of dopamine, norepinephrine, and serotonin, are both CNS active drugs with the potential to cause adverse outcomes or irreversible effects on learning/memory/behavioral development as a result of exposure during the pre-pubertal/pubertal period. The sponsor has proposed to conduct a juvenile rat study with dosing beginning on PND 7 and continuing for 8 weeks followed by a 2-week recovery period prior to the initiation of the Phase 3 pediatric studies. Specific endpoints that will be addressed include standard clinical pathology and toxicity endpoints, behavior (open field), learning and memory (passive avoidance and water maze), long bone growth, sexual maturation, mating and fertility, reversibility of toxicity after a drug-free period, and toxicokinetic exposure assessment.

The Division agrees that a juvenile study is appropriate given the stated concerns, and has developed a general juvenile protocol for other obesity drugs that modulate neurotransmitter activity. The major active metabolite of bupropion in humans, which has CNS activity, is made in the mouse but present only in small amounts in rats. Therefore, it is recommended that the studies be conducted in prepubertal/pubertal mice; this is in agreement with the recommendations of the EMA's Pediatric Committee (PDCO). It is also recommended that a motor activity test, FOB testing, and two learning tests (e.g., acoustic startle pre pulse inhibition and water maze tests) be conducted. The learning tests would be conducted in a cohort during the treatment (not included in proposed study) and in a separate cohort after a post-recovery phase to assess reversibility of any observed treatment effect. We agree with the sponsor's additional assessments for bone growth, sexual maturation, and mating/fertility.

Clinical Studies:

Clinical studies will be conducted in a step-wise approach with studies conducted first in adolescent patients.

1. PK/PD/safety study in adolescents
 - a. Single and multiple-dose pharmacokinetic and tolerability study in adolescents ages 12 - 17 years. This can be a substudy that leads into the safety and efficacy study so that subjects in the PK study (b) (4) roll-over into the PD/safety portion of the trial.
 - b. One-year safety and efficacy study in adolescents ages 12 – 17 years.
2. PK/PD/safety study in children
 - a. Single and multiple-dose pharmacokinetic and tolerability study in children ages 7 to 11 years. This can be a substudy that leads into the safety and efficacy study so that subjects in the PK study (b) (4) roll-over into the PD/safety portion of the trial.
 - b. One-year safety and efficacy study in children ages 7 to 11 years.

Clin. Pharm. Comments: The proposed plan is reasonable for both the age groups. However, sponsor should conduct the PK and tolerability part as a substudy with a definite plan to roll-over these pediatric subjects in safety and efficacy study instead of the proposed

(b) (4)

Age group and population (indication) in which study will be performed:

This section should list the age group and population exactly as it is in the plan.

1. The company proposes a population of pediatric patients with obesity, ages ≥ 12 to ≤ 17 years, with one or more weight-related comorbidities (controlled hypertension, diabetes, or dyslipidemia) with BMI above the 95th percentile based on age and sex and not greater than 44 kg/m^2 . Subjects with genetic or endocrine causes of obesity will be excluded.

DMEP agrees with this population but adds that adequate representation from both male and female adolescents should be included and subjects must have a documented history of failure to lose sufficient weight with lifestyle modification alone.

2. The company proposes a population of pediatric patients with obesity, ages ≥ 7 to ≤ 11 years, with BMI above the (b) (4) percentile [redacted] Subjects with genetic or endocrine causes of obesity will be excluded.

DMEP proposes the following: Children, ages 7 - 11 years (inclusive) with age- and sex-matched BMI ≥ 99 th percentile with a major co-morbidity. Subjects must have a documented history of failure to lose sufficient weight with comprehensive multidisciplinary intervention. Subjects with obesity associated with known endocrine or genetic causes will be excluded.

Number of patients to be studied or power of study to be achieved:

Study 1: 300 subjects randomized to one of two treatment arms of either placebo or active doses of naltrexone/bupropion

Study 2: To be determined

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients must have a negative pregnancy test if female..

Clinical endpoints:

The company proposes the following endpoints: The primary efficacy endpoint is percent of subjects achieving 5% reduction in BMI. Examples of key secondary endpoints include percentage change in BMI, proportion of subjects achieving reductions in BMI of 10% or

more, effects on blood pressure, lipid and glycemic variables, waist circumference, and safety parameters.

DMEP: These endpoints are acceptable. BMI should be adjusted for age and sex. Safety assessments should include monitoring for heart rate changes and neurocognitive adverse effects.

Example:

Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):

Example:

Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.

Division comments on product safety:

Are there any safety concerns currently being assessed? Yes No

1. Cardiovascular (increased blood pressure and heart rate)

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? Yes No

Will a DSMB be required? Yes No

Other comments: The side effect profile of naltrexone/bupropion is consistent with the known adverse effects of the individual components. In a safety cohort of approximately 3200 overweight and obese adults treated with the naltrexone/bupropion combination, there was a higher incidence of cardiac-related adverse events (blood pressure increased, palpitations), psychiatric disorders (mostly related to insomnia and anxiety), neurocognitive disorders (such as dizziness, syncope, attention disorder), small increases in serum creatinine, and tolerability-related issues (such as nausea, vomiting, headache) compared to placebo-treated individuals. Suicidality was assessed prospectively using the C-SSRS questionnaire. No suicidality signal has been observed in this program. The LS mean change in systolic blood pressure by ambulatory blood pressure monitoring was 2.6 mm Hg higher in the Contrave group compared to the placebo group at Week 52.

Division comments on product efficacy:

Contrave, the fixed dose combination of naltrexone and bupropion, has established clinically and statistically significant weight loss in overweight and obese adults, meeting the Division's current benchmarks for weight loss efficacy. In overweight or obese adults with 2 or more weight-related comorbidities, there was a greater proportion of subjects treated with Contrave who achieved $\geq 5\%$ weight loss from baseline compared with the placebo group. Improvements were also noted in waist circumference, glycemic control, triglycerides, and HDL.

Division comments on sponsor proposal to satisfy PREA:

Conducting studies as revised by the Division should satisfy PREA.

PeRC ASSESSMENT TEMPLATE

Please attach:

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC? **Yes** **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols*.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:

Example:

Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):

This section should list the statistical tests conducted.

Example:

Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Timing of assessments:

Example:

Baseline, week 2, week, 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

PATRICIA J MADARA
05/06/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (contrave) Request for Information
Date: Friday, April 11, 2014 11:26:00 AM
Attachments: [11April14 Contrave info request.pdf](#)
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have additional requests for information:

Please respond to the items listed in the attached PDF document.

You may submit your responses informally, via email but also send them officially to the NDA.

We request a response by Friday, April 18, 2014, in order to continue our evaluation of your NDA.

Thanks for your help. **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

Reference is made to your resubmission of NDA 200063 for CONTRAVE extended release tablets dated December 10, 2013 and the Data Access Plan Version 2.0 submitted February, 7, 2014. Please provide the information, as specified below, regarding who has knowledge of or access to unblinded data or analysis results of the ongoing LIGHT cardiovascular outcomes trial. In order to conduct our review in a timely manner, please respond to this information request by Friday, April 18, 2014:

1. Submit a list of all individuals, excluding members of the Data Monitoring Committee, with access or knowledge of the unblinded data or unblinded analysis results of the LIGHT trial. Please specify in this list the function, level of data access (based on Table 1 of the Data Access Plan), and company or affiliation for these individuals. This list may be provided in tabular form as shown in the example below:

Name	Function	Data Access Level	Affiliation
John Doe	Statistician	Full access	(b) (4)

2. Please clarify if each individual with unblinded data access or knowledge of unblinded study results signed a confidentiality agreement. If so, please provide such information.

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/s/

PATRICIA J MADARA
04/11/2014



NDA 200063

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Orexigen Therapeutics, Inc.
3344 North Torrey Pines Court, Suite 200
La Jolla, CA 92037

ATTENTION: Thomas Bicsak, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Bicsak:

Please refer to your New Drug Application (NDA) dated December 10, 2013, and received December 11, 2013, submitted under section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act for Naltrexone and Bupropion Extended-Release Tablets, 8 mg/90 mg.

We also refer to your January 27, 2014, correspondence, received January 27, 2014, requesting review of your proposed proprietary name, Contrave. We have completed our review of the proposed proprietary name, Contrave and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 27, 2014, 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 Terrolyn Thomas, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Patricia Madara, Senior Regulatory Project Manager, in the Office of New Drugs at (301)796-1249.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/03/2014

From: Madara, Patricia
To: ["Teri Johnson"](#)
Subject: RE: 14-Mar-14 NDA 200063 (Contrave) Request for clarification - question #7
Date: Monday, March 24, 2014 2:28:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have additional requests for information:

Finally, we also reference your responses to our information requests issued on March 14, 2014, via email. Your responses are attached below to this email.

We have the following request for clarification related to your response to question #7 regarding the SAE tables:

1. For the Study NB-CVOT CSR Tables 28 and 14.3.1-1.1, you provided the following in a footnote:
 - "Treatment-emergent SAEs were defined as SAEs with onset coincident with treatment period randomization starting at Day 1 and through end of study or 30 days after discontinuation of study medication (whichever one is later), and existing SAEs that worsened during the treatment period."
2. We have interpreted that statement to mean that a subject who discontinued study drug at Day 60 but was continuing to be followed in the trial and experienced an SAE on Day 120, that the SAE at Day 120 would still be included in the table as they are still in the study. According to your response today, it sounds like that subject's SAE would only be included if it occurred prior to Day 91.

Please confirm if this is correct.

We request a prompt response in order to continue our evaluation of your NDA.

Thanks for your help. **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

From: Teri Johnson [mailto:tjohnson@orexigen.com]
Sent: Monday, March 24, 2014 9:50 AM
To: Madara, Patricia
Subject: 14-Mar-14 NDA 200063 (Contrave) Requests for Information - OREX Response (Q2 & 7)

Hi Pat –

Please find responses below to Items 2 & 7 contained in the clinical information request document. To get these over to you as quickly as possible we are providing these via e-mail as a review aid. These responses will be sent to the NDA.

14 March 2014 Clinical Information Requests

2. In Table 14.3.1-1.1. under the General Disorders and Administration Site Conditions SOC, there 8 deaths listed: death ((b) (4) accidental death (b) (4) sudden cardiac death ((b) (4)). Do these 8 deaths correspond to the following subjects that are listed as non-CV deaths : Subject Numbers 10620018, 10800045, 11500034, 10020052, 10490064, 11480125, 11520031 and 11970055?

The 8 deaths summarized in the General Disorders and Administration Site Conditions SOC do not directly correspond to the non-CV deaths specified above.

All deaths whether reported as a death verbatim or as an event with death as an outcome are recorded as an SAE and proceed to adjudication. These events are summarized within the appropriate SOC according to their preferred term regardless of the adjudication outcome. Importantly, it is during the adjudication process that the adjudicators determine which events are non-CV deaths and therefore there will not in every instance be a direct relationship between SOC categorization and adjudication categorization.

The 8 deaths summarized in the General Disorders and Administration Site Conditions SOC in Table 14.3.1-1.1, correspond to adjudicated outcome as categorized in Table 1:

Table 1: Subjects with deaths represented under the General Disorders and Administration Site Conditions SOC in Study NB-CVOT CSR Table 14.3.1-1.1

Subject Number	Treatment	Preferred Term	Adjudicator Decision
11970055	(b) (4)	Death	Non-CV death
10740008	(b) (4)	Death	CV death
11480089	(b) (4)	Death	CV death
10780044	(b) (4)	Death	Pending
11870025	(b) (4)	Death	CV death
12280003	(b) (4)	Death	CV death
12790015	(b) (4)	Accidental death	Pending
10350035	(b) (4)	Sudden cardiac death	CV death

As stated in the question, there are 8 subjects listed as having non-CV deaths, one of which is subject number 11970055 shown in Table 1. The remaining 7 subjects in the question and corresponding detail are shown in Table 2.

Table 2: Subjects with deaths adjudicated as non-CV death that are not represented under the General Disorders and Administration Site Conditions SOC in Study NB-CVOT CSR Table 14.3.1-1.1

Subject Number	Treatment	Preferred Term	System Organ Class	Adjudicator Decision
10620018	(b) (4)	Sepsis	Infections and Infestations	Non-CV death
10800045	(b) (4)	Road traffic accident	Injury, Poisoning and Procedural Complications	Non-CV death
11500034	(b) (4)	Gun shot wound	Injury, Poisoning and Procedural Complications	Non-CV death
10020052	(b) (4)	Gun shot wound	Injury, Poisoning and Procedural Complications	Non-CV death
10490064	(b) (4)	Pancreatic carcinoma	Neoplasms Benign, Malignant and Unspecified	Non-CV death
11480125	(b) (4)	Cardio-respiratory arrest Metastatic cancer of	Cardiac Disorders Neoplasms Benign, Malignant	Non-CV death

	(b) (4)	unknown origin	and Unspecified	
11520031		Death	General Disorders and Administration Site Conditions*	Non-CV death

* Subject not included in Table 14.3.1-1.1 summary because this event was not treatment emergent.

7. Provide an SAE table by SOC and Preferred Term for SAEs that have occurred up to and including 30 days after a subject's last confirmed treatment period dose date (on-treatment data).

Study NB-CVOT CSR Tables 28 and 14.3.1-1.1 contain tables by SAE SOC and Preferred Term for SAEs that have occurred up to and including 30 days after a subject's last confirmed treatment period dose date (on-treatment data).

Please do not hesitate to let me know if there any additional questions. We will send responses to the remaining items as soon as possible.

Kind regards,
Teri

From: Madara, Patricia [<mailto:Patricia.Madara@fda.hhs.gov>]
Sent: Friday, March 14, 2014 7:45 AM
To: Teri Johnson
Subject: NDA 200063 (Contrave) Requests for Information
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have additional requests for information:

- 1. Please respond to the attached PDF document containing clinical information requests.**
- 2. Your (b) (4) the pediatric plan submitted on December 20, 2013, proposes studies in children 12-17 and 7-11 years of age. (b) (4) Please submit updated pediatric waiver and deferral requests that are in alignment with the more recently submitted pediatric plan.**

You may submit your responses informally, via email but also send them officially to the NDA.

We request a prompt response in order to continue our evaluation of your NDA.

Thanks for your help. **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

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/s/

PATRICIA J MADARA
03/25/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Request for Information
Date: Friday, March 21, 2014 6:30:00 PM
Attachments: [21March14 clinical request for information.pdf](#)
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have additional requests for information:

- 1. Please respond to the attached PDF document containing clinical information requests.**
- 2. Please provide the rationale for the decision to conduct studies in (b) (4) to support pediatric development under the EMA whereas juvenile studies in rats are proposed in your PPSR for NDA 200063.**

You may submit your responses informally, via email but also send them officially to the NDA.

We request a prompt response in order to continue our evaluation of your NDA.

Thanks for your help. **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

Contrave NDA 200063 Information Request 3/20/14

Please provide the following:

For the ITT Population and the PP population, the proportion of subjects achieving $\geq 5\%$ weight loss from baseline to Week 26 and baseline to Week 52. The table below is an example.

	ITT Population (with LOCF)		PP Population	
	Placebo (N=4450)	NB (N=4455)	Placebo (N=4354)	NB (N=4366)
Subjects with Weight Measurement at Week 26				
Proportion of Subjects Achieving $\geq 5\%$ Weight Loss, n (%)	n (%)			
95% CI				
Odds Ratio (95% CI) ¹				
p-value ¹				
Subjects with Weight Measurement at Week 52				
Proportion of Subjects Achieving $\geq 5\%$ Weight Loss, n (%)				
95% CI				
Odds Ratio (95% CI) ¹				
p-value ¹				

Note: Odds ratio is NB relative to placebo (placebo in the denominator).

¹ Based on a logistic regression model with treatment, cardiovascular risk group, race grouping (white, non-white) and sex as factors, and body weight at baseline and age as covariates.

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/s/

PATRICIA J MADARA
03/24/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Requests for Information
Date: Friday, March 14, 2014 10:44:00 AM
Attachments: [14March14 Information Request.pdf](#)
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have additional requests for information:

- 1. Please respond to the attached PDF document containing clinical information requests.**
- 2. Your [REDACTED] (b) (4) the pediatric plan submitted on December 20, 2013, proposes studies in children 12-17 and 7-11 years of age. [REDACTED] (b) (4) Please submit updated pediatric waiver and deferral requests that are in alignment with the more recently submitted pediatric plan.**

You may submit your responses informally, via email but also send them officially to the NDA.

We request a prompt response in order to continue our evaluation of your NDA.

Thanks for your help. **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

Information Request for NDA 200063 Contrave

- 1) There are (b) (4) deaths that have undergone adjudication (b) (4) but there are only (b) (4) narratives of death included in Section 14.3.3.1. Where are the remaining (b) (4) death narratives?
- 2) In Table 14.3.1-1.1. under the General Disorders and Administration Site Conditions SOC, there 8 deaths listed: death (b) (4) accidental death (b) (4) sudden cardiac death (b) (4) Do these 8 deaths correspond to the following subjects that are listed as non-CV deaths : Subject Numbers 10620018, 10800045, 11500034, 10020052, 10490064, 11480125, 11520031 and 11970055?
- 3) Disposition for the ITT population: For the categories of “subject decision to no longer receive study medication” and “lost to follow-up”, please provide more specific information on what reasons the subjects gave for discontinuation, the time course for these discontinuations, and the breakdown by site.
- 4). Subject 10940004 ((b) (4) Site 1094, PI Alan Wiseman): Please provide any updated information on this case. Include an explanation for why appropriate laboratory tests such as bilirubin and hepatitis serologies were not evaluated in this case and what steps have been taken to ensure this does not occur in future cases.
- 5) Subject 11060022 ((b) (4)): AE of hepatic cirrhosis which led to study drug discontinuation. Please provide any updated information on this case. The subject had baseline blood pressure of 114/63 mmHg and the following values at subsequent visits: Week 2, 154/63; Week 8, 143/62; Week 16, 134/77; Week 16 Evaluation Recheck, 117/65; Week 26, 157/73. Was this subject counted as having sustained increases (≥ 2 consecutive measurements) in systolic blood pressure of ≥ 10 mm Hg at any time?
- 6) For Section 12.2.3.2 Analysis by Special Topics, please provide your method of categorizing the adverse events of special interest. For example, in Section 12.2.3.2.5 *Hypersensitivity, Including Skin Rash* on page 147 of 181 of the NB-CVOT study report, explain how the collection of preferred terms was determined. Is this based on a MedDRA SMQ or is it similar to the method used in the original submission for the Special Topic categories which comprised all preferred terms present in the database which had been prespecified, along with relevant additional terms needed to fully describe the medical concept.
- 7) Provide an SAE table by SOC and Preferred Term for SAEs that have occurred up to and including 30 days after a subject’s last confirmed treatment period dose date (on-treatment data).
- 8) Please provide the following CV adjudication packages:
 - Subject: NB-CVOT-1140-11400019 AE term: Myocardial infarction (b) (6)
 - Subject: NB-CVOT-1148-11480125 AE term: Cardio-respiratory arrest (b) (6)

- Subject NB-CVOT-1090-10900052 AE term: Transient ischaemic attack (b) (6)
- Subject NB-CVOT-1209-12090001 AE term Chest pain (b) (6)
- Subject NB-CVOT-1002-10020005 AE term Angina pectoris (b) (6)
- Subject NB-CVOT-1002-10020059 AE term Angina unstable (b) (6)
- Subject NB-CVOT-1115-11150001 AE term OLD LACUNAR INFARCT OF THE LEFT THALAMUS
Lacunar (b) (6)
- Subject NB-CVOT-1164-11640026 AE term DEATH -UNKNOWN CAUSE (b) (6)
- Subject NB-CVOT-1229-12290006 AE term Coronary artery disease (b) (6)

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/s/

PATRICIA J MADARA
03/14/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Request for Information
Date: Monday, February 03, 2014 8:00:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application and have the following requests for information:

- 1. Please clarify whether SAEs referred for adjudication could be modified after adjudication (i.e., if an investigator reports MI and the adjudication committee downgrades it to non-cardiac chest pain, does the AE dataset still say MI?).**
- 2. Please submit the minutes of all steering committee and DMC meetings (open & closed).**
- 3. Please submit the AE terms that you used to search for potential endpoint events that may not have been flagged by an investigator. We would like the AE terms submitted in both a pdf file and a SAS transport file.**

You may submit your responses informally, via email but also send them officially to the NDA. We request a prompt response in order to continue our evaluation of your NDA.

Thanks for your help. **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

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/s/

PATRICIA J MADARA
02/03/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) - Request for Information
Date: Tuesday, January 21, 2014 5:10:00 PM
Attachments: [21Jan14_email_Questions_for_Sponsor.pdf](#)
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We continue to review your application. Please see the attached PDF document for our comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Thanks for your help. **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

NDA 200063 Questions for Sponsor

Question 1: Please explain why the discontinuations at Week 16 from the DMC Closed Report (shown below) of Pbo 40.7; NB 14.2% are different than what is shown in the NB-CVOT Table 14.2-16 (Pbo 43.4%; NB 17.0%)?

Subject Disposition and Reasons for Discontinuation (ITT)

Subject Disposition	Placebo (N = 4450) n (%)	Contrave (N = 4455) n (%)
Continuing treatment with study medication	1201 (27.0%)	1709 (38.4%)
Discontinued treatment with study medication	3249 (73.0%) ¹	2746 (61.6%)
Adverse event	330 (7.4%)	1188 (26.7%)
Not meeting Week 16 continuation of treatment criteria	1809 (40.7%)	633 (14.2%)
Subject decision to no longer receive study medication	778 (17.5%)	613 (13.8%)
Lost to follow up ²	162 (3.6%)	158 (3.5%)
Other	117 (2.6%)	126 (2.8%)
Protocol deviation	27 (0.6%)	14 (0.3%)
Sponsor decision	25 (0.6%)	14 (0.3%)

Source: DMC Closed Report Table 2

1 One subject did not have a reason for study medication discontinuation specified

2 Subjects for whom contact was not possible when a visit was missed were designated as lost to follow up for this category. They may still be followed via alternative contact (e.g., family, friend, physician).

NB-CVOT Table 14.2-16: Week 16 Continuation of Treatment Assessment in Study NB-CVOT (ITT Population)

	Placebo (N=4450) n (%)	NB32 (N=4455) n (%)	Total (N=8905) n (%)
Subjects Discontinued by Investigator Due to Week 16 Assessment ¹	1930 (43.4%)	759 (17.0%)	2689 (30.2%)
<2% Weight Loss Only	1678 (37.7%)	568 (12.7%)	2246 (25.2%)
BP Outlier Only	10 (0.2%)	49 (1.1%)	59 (0.7%)
<2% Weight Loss and BP Outlier	222 (5.0%)	111 (2.5%)	333 (3.7%)
Other ²	20 (0.4%)	31 (0.7%)	51 (0.6%)

Data Source: NB-CVOT Table 14.2-16.

Abbreviations: BP=blood pressure.

1 Evaluation to Continue Treatment Case Report Form

2 Other reason can be Incomplete Data (ie, missing body weight and/or blood pressure data at Week 16), Inconsistent Data (ie, recorded data do not support the decision), or Incorrect CRF Entry (ie, Week 16 assessment CRF should not have been completed), but cannot be <2% weight loss and/or blood pressure outliers (including rechecks).

Note: Blood pressure outlier is blood pressure increase by 10 mmHg or more from baseline at Weeks 8 and 16 (including recheck), or at Weeks 2 and 16 (including rechecks) if Week 8 is missing.

Question 2: Regarding the definition of the on treatment ITT population: In your document you describe this population as subjects who received at least one dose of randomized study medication

during the treatment period with the exclusion of data from >30 days past the last dose of study medication for subjects who discontinued treatment. This does not sound like it is the group of subjects who remain on study drug throughout the entire evaluation period. Please clarify if this is correct. If so, will you also be describing the results for the subjects who remain on study drug throughout the evaluation period (such as a “completer’s population”).

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/s/

PATRICIA J MADARA
01/21/2014

From: Madara, Patricia
To: [Teri Johnson \(tjohnson@orexigen.com\)](mailto:tjohnson@orexigen.com)
Subject: NDA 200063 (Contrave) Request for Information
Date: Monday, January 06, 2014 4:17:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

In addition, reference is made to your resubmission dated December 10, 2013. We have requests for information regarding the cardiovascular outcomes trial (CVOT) and the interim analysis to rule out the 2.0 risk margin. In order to conduct our review in a timely manner, please address these information requests according to the timelines specified:

Please respond to the following within 7 business days of this information request:

1. Specify the data cut-off and database lock dates for the above referenced interim analysis.
2. Submit the DMC meeting minutes corresponding to the above referenced interim analysis.
3. We are unable to locate the final charter for the Clinical Events Committee for the CVOT in your resubmission of the NDA. Please submit this document, or provide the location if it is already included in your resubmission.

Please respond to the following by the date that you submit your full interim analysis study report:

-

Include in your interim analysis study report subgroup analyses of the primary endpoint by baseline demographic characteristics (age, gender, and race) as well as by baseline cardiovascular risk factors.

On page 16 of your Data Monitoring Committee charter (dated August 7, 2013) you note that a Data Access Plan will be created to ensure that only the unblinded team members will have access to the unblinded interim data for the CVOT. Please provide details of the firewall procedures that were implemented and submit the Data Access Plan.

Thanks for your help. **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

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/s/

PATRICIA J MADARA
01/06/2014

From: Madara, Patricia
To: ["Teri Johnson"](#)
Subject: NDA 200063 (Contrave) - Request for Information
Date: Friday, December 20, 2013 12:00:00 PM
Importance: High

NDA 200063

INFORMATION REQUEST

Hi Teri:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion)

We also refer to your December 10, 2013, submission, containing a complete, class 2 resubmission.

We are beginning to review your application and have the following comments and information requests. We request a prompt written response in order to continue our evaluation.

- **We appreciate your submission of the clinsite.xpt dataset for use in CDER's Clinical Site Selection Tool. However, several of the variables needed to use the tool are missing. Please consider resubmission of the clinsite.xpt dataset including the following variables:**

- 1. LASTNAME**
- 2. FRSTNAME**
- 3. MINITIAL**
- 4. PHONE**
- 5. FAX**
- 6. EMAIL**
- 7. COUNTRY**
- 8. STATE**
- 9. CITY**
- 10. POSTAL**
- 11. STREET**
- 12. NDA**

Thanks for your help. **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

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/s/

PATRICIA J MADARA
12/20/2013



NDA 200063

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Orexigen Therapeutics, Inc.
Attention: Thomas Bicsak, Ph.D.
Vice President, Regulatory Affairs
3344 N. Torrey Pines Court, Suite 200
La Jolla, CA 92037

Dear Dr. Bicsak:

We acknowledge receipt on December 10, 2013, of your December 10, 2013, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Contrave (8 mg naltrexone HCl / 90 mg bupropion HCl) extended release tablets.

We consider this a complete, class 2 response to our January 31, 2011, action letter. Therefore, the user fee goal date is June 10, 2014.

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

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/s/

PATRICIA J MADARA
12/20/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200063

MEETING MINUTES

Orexigen Therapeutics, Inc.
Attention: Thomas Bicsak
Vice President, Regulatory Affairs
3344 North Torrey Pines Court
La Jolla CA 92037

Dear Mr. Bicsak:

Please refer to your New Drug Application (NDA) dated DATE, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave® (naltrexone HCl and bupropion HCl) Tablet.

We also refer to the meeting/telecon between representatives of your firm and the FDA on October 24, 2013. The purpose of the meeting was to seek an agreement on the proposed products dissolution specification for Contrave.

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

If you have questions, call me at (240)-402-3722

Sincerely,

{See appended electronic signature page}

Priyanka Kumar, Pharm. D
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
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: Type C

Meeting Date and Time: October 24, 2013
Meeting Location: Teleconference

Application Number: 200063
Product Name: Contrave ® (naltrexone HCl and bupropion HCl) Tablet
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss.

Sponsor/Applicant Name: Orexigen Therapeutics, Inc.

Meeting Chair: Tapash Ghosh
Meeting Recorder: Priyanka Kumar

FDA ATTENDEES

John Duan, Ph.D. Pharmacologist, ONDQA
Tapash Ghosh, Ph.D. Biopharmaceutics Lead, ONDQA
Priyanka Kumar, Pharm.D. Regulatory Project Manager, ONDQA
Rebecca McKnight, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES

(b) (4)

Thomas Bicsak, PhD, Vice President, Regulatory Affairs, Orexigen Therapeutics, Inc.
Sandra Cosner, RPh Associate Director, Regulatory Affairs, Takeda Development Center Americas, Inc.
Amy Halseth, PhD, Director, Clinical Science Orexigen Therapeutics, Inc.
Teri Johnson, RAC, Director, Regulatory Affairs, Orexigen Therapeutics, Inc.
Philip Roberts, MS, Vice President, Technical Operations, Orexigen Therapeutics, Inc.
Jennifer Stanek, Associate Director, Regulatory Affairs CMC, Takeda Development Center Americas, Inc.
Min Xia, PhD, Sr. Director, Analytical Dev and Control Orexigen Therapeutics, Inc

1.0 BACKGROUND

The purpose of the Type C meeting is to seek agreement on the proposed product dissolution specification for Contrave, based on the Agency's recommendations on this issue identified in the 31 January 2011 Complete Response Letter (CRL), prior to the NDA resubmission. Contrave: Naltrexone HCl/bupropion HCl extended-release tablets. If indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification. The Agency has proposed a revised dissolution specification for Contrave in the 31 January 2011 Complete Response Letter (CRL); see Section 8.1. Orexigen has evaluated the Agency-proposed changes to the product *in vitro* dissolution specifications employing comprehensive statistical analysis of relevant clinical Phase 3 and Phase I (bioavailability) lots, and believes that a further refined specification would more appropriately support current product characteristics and performance while adhering to regulatory guidance.

2. DISCUSSION

2.1. Category/Discipline A

1. **Question 1:** *Does the Division agree with the revised dissolution specification as proposed by Orexigen?*

FDA Response to Question 1: No, we do not agree with the revised dissolution specification. You did not provide sufficient justification for the proposed revision of the dissolution specifications. Revise your proposal based on the recommended acceptance criteria. Note the following comments:

- The observed *in vitro* variability is relevant to the product's *in vivo* performance.
- You stated that small differences in API release in the *in vitro* setting are unlikely to meaningfully impact overall *in vivo* systemic exposure to the pharmacologically active moieties. The "small differences" were not defined. The differences should not be larger than the limits, which assure bioequivalence between the to-be-marketed lots and the clinical lots. Without a validated IVIVC, the dissolution limits are generally $\pm 10\%$ from the mean.
- The statistical method and the data for determination of the tolerance intervals should be provided.
- The 1 h time point should be selected.
- Dissolution acceptance criteria should be set based on the mean, not the (b) (4)

ADDITIONAL COMMENT

1. We acknowledge the data from the *in vitro* alcohol interaction study that you submitted in this meeting package. Based on these data, we agree that your proposed product does not

demonstrate dose dumping in the presence of alcohol. Please submit these data in your complete response for this NDA.

Discussion:

- The Agency stated that setting the dissolution acceptance criteria are based on the mean values, not the [REDACTED] (b) (4). Therefore, it is not a failure if some batches go to Stage II when the dissolution testing is performed.
- The acceptance criterion at any dissolution time point should be $\pm 10\%$ from the mean dissolution profile obtained from the pivotal clinical study batches, which are the standard for comparison. The dissolution of the to-be-marketed formulation should meet these criteria to assure the bioequivalence to the pivotal clinical study batches. If an IVIVC is approved, it can be used to justify wider acceptance criteria.
- The Agency indicated that the dissolution data showed in vivo relevance, which may serve a starting point to explore a potential IVIVC. If an IVIVC is not feasible, an IVIVR may be helpful for further drug development.
- The Applicant requested the rationale for selection of the one-hour time point. The Agency responded that all three phases of release should be captured and the 1-hour time point represents the release during the middle phase.

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/s/

PRIYANKA KUMAR
11/12/2013



NDA 200063

MEETING REQUEST GRANTED

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines Court, Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.

We also refer to your December 19, 2012, correspondence requesting a guidance meeting to discuss the proposed content of the NDA resubmission. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The teleconference is scheduled as follows:

Date: March 11, 2013
Time: From 2:00 pm to 3:00 pm
Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

FDA ATTENDEES (Tentative):

Office of Drug Evaluation II/Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D., Division Director
Eric Colman, M.D., Deputy Division Director
James Smith, M.D., Medical Officer
Eileen Craig, M.D., Medical Officer
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Julie Marchick, M.P.H., Chief Project Management Staff
Amy Egan, M.D., Deputy Division Director for Safety Deputy Director

Division of Biometrics VII (DB VII), Office of Biostatistics

Xiao Ding, Ph.D., Biometrics Reviewer
Mat Soukup, Ph.D., Biometrics Team Leader
Aloka Chakravarty, Ph.D., Division Director

Division of Biometrics II (DB II), Office of Biostatistics

Jon (Todd) Sahlroot, Ph.D., Deputy Division Director and Statistics Team Leader
Janice Derr, Ph.D., Biometric reviewer

Office of Surveillance and Epidemiology

Ermias Zerislassie, Pharm.D., M.P.H., Safety Regulatory Project Manager

Controlled Substance Staff

Chad Reissig

Submit background information for the meeting (three paper copies or one electronic copy to the application and 16 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by February 11, 2013, we may cancel or reschedule the meeting.

Submit the 16 desk copies to the following address:

Meghna M. Jairath, Pharm.D.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3387
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, 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/

MEGHNA M JAIRATH
01/25/2013



NDA 200063

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines, Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended Release tablets, 8mg/90mg.

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

¹ These violations include studies conducted by (b) (4) specific to the (b) (4)

searching available documentation to determine which NDAs are impacted by the above findings.

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, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

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

09/08/2011

J. Marchick signing for M. Parks

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: IR: NDA 200063 Contrave _January 7_2010
Date: Friday, January 07, 2011 9:00:44 AM

NDA 200063

Dear Ms. Johnson:

The following **information request (IR)**. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266

Respond by: January 10, 2010

1. Please submit the following:

In the opinion and to the best knowledge of your knowledge (*name of applicant*), there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs to address your reliance on ReVia. Refer to 21 CFR 314.50(i)(1)(ii).

Please confirm receipt of this email.

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
01/07/2011

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: Information request_NDA 200063_ License Agreement
Date: Monday, January 03, 2011 3:56:09 PM

Hi Teri,

Please submit the following statement to the NDA, from the patent owner, stating that it has a licensing agreement with Orexigen and that it consents to an immediate effective date according to 21 CFR 314.50(i)(3).

The full reg:

(3)Licensing agreements. If a 505(b)(2) application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant shall submit a certification under paragraph (i)(1)(i)(A)(4) of this section ("Paragraph IV Certification") as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the 505(b)(2) application, the application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

Thanks.

Meghna

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/s/

MEGHNA M JAIRATH
01/03/2011

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: December 1, 2010 at 1:30 pm
Meeting Location: Teleconference

Application Number: NDA 200063
Product Name: Contrave (naltrexone HCl/bupropion HCl) extended release tablets, 4 mg/90 mg and 8 mg/90 mg.
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss.
Sponsor/Applicant Name: Orexigen Therapeutics, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

FDA ATTENDEES

Eric Colman, M.D. Deputy Director, Division of Metabolism and Endocrinology Products (DMEP)
Meghna M. Jairath, Pharm.D. Regulatory Project Manager, DMEP
Curt Rosebraugh, M.D. Director of Office of Drug Evaluation II
Mary Parks, M.D. Division Director, DMEP
Amy Eagan, M.D. Safety Deputy Director, DMEP
Lina AlJuburi, Pharm.D., M.S. Chief, Project Management Staff, DMEP

SPONSOR ATTENDEES

Orexigen

Dawn Viveash, M.D. Sr. VP, Head, Global Quality, Regulatory Affairs and Safety
Teri Johnson, RAC Director, Regulatory Affairs and Development Strategic
Preston Klassen, MD, MHS Sr. VP, Head of Development
Eduardo Dunayevich, M.D. Chief Medical Officer
Wendy Wang Sr. VP, Head of Global Biomedical Information

Takeda Global Research & Development

Lawrence Roebel Sr. Director Regulatory Affairs
Thomas Strack, MD Vice President, Clinical Science

1.0 BACKGROUND

The Division has serious concerns about Contrave's pressor effects, particularly in light of the results of SCOUT, and wanted the sponsor to present their interpretation of the blood pressure and pulse data to the Division. The sponsor presented this information on October 13, 2010.

We had a follow up teleconference with the sponsor on October 18, 2010 to their formal presentation on October 13, 2010. We informed the sponsor that they should submit a design of an outcomes trial. The sponsor had indicated that they will be submitting an updated risk mitigation plan to us in addition to the outcomes trial design.

On November 3, 2010, via email, the sponsor submitted their Cardiovascular (CV) and REMS proposal. We had a follow up teleconference with the sponsor on November 10, 2010 to discuss their CV proposal. We informed the sponsor that they should submit a detailed design of an outcomes trial which could include both randomized and observational approaches prior to the Advisory Committee meeting scheduled on December 7, 2010.

In regards with the sponsor's REMS proposal we sent them an email correspondence on November 17, 2010.

On November 29, 2010, via email, the sponsor submitted their detailed design of their CV outcomes proposal. This teleconference is to follow-up with the sponsor about our recommendations on their current CV safety proposal.

2 DISCUSSION

We informed the sponsor that after reviewing their CV outcomes proposal we do not agree with them doing an (b) (4). We stated that they should do a controlled randomized trial.

We also stated that discussion on details of the randomized trial design being a pragmatic vs. traditional should not be discussed at the upcoming AC meeting. The details of an adequately designed controlled trial can occur with us post meeting. The sponsor was in agreement with this approach.

We also stated to the sponsor that they should concentrate on presenting the data they have at hand to allow them to conduct a trial to allow marketing of this product.

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/s/

MEGHNA M JAIRATH
12/03/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
cc: [Aljuburi, Lina;](#)
Subject: NDA 200063_Clinical IR_11_29_10
Date: Monday, November 29, 2010 4:16:11 PM
Attachments: [NDA 200063 clinical IR on Medication Query 11 29 10.pdf](#)

NDA 200063

Dear Ms. Johnson:

The following **information request (IR)** is from our Clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266

Respond by: November 30, 2010

Please see attachment for IR.

Please confirm receipt of this email.

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)

Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
11/29/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
cc: [Aljuburi, Lina;](#)
Subject: NDA 200063_Clinical_11_23_10
Date: Tuesday, November 23, 2010 11:51:14 AM
Attachments: [NDA 200063 Clinical questions 11-23-2010.pdf](#)

NDA 200063

Dear Ms. Johnson:

The following **information request (IR)** is from our Clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266

Respond by: November 24 , 2010

Please see attachment for IR.

Please confirm receipt of this email.

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)
[Center for Drug Evaluation and Research](#)

Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
11/23/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: FDA REMS Response NDA 200063 (Contrave)
Date: Wednesday, November 17, 2010 2:39:01 PM
Attachments: [REMS proposal FDA resp.pdf](#)

Hello,

Please see the attachment for our response to your proposed REMS proposal.

Please confirm receipt of the email.

Thanks.

Meghna

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/s/

MEGHNA M JAIRATH
11/17/2010

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: November 11, 2010

Application Number: NDA 200063
Product Name: Contrave (naltrexone HCl/bupropion HCl) extended release tablets, 4 mg/90 mg and 8 mg/90 mg. [Insert product name]
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss.
Sponsor/Applicant Name: Orexigen Therapeutics, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

FDA ATTENDEES

Eric Colman, M.D. Deputy Director, Division of Metabolism and Endocrinology Products (DMEP)
Meghna M. Jairath, Pharm.D. Regulatory Project Manager, DMEP

SPONSOR ATTENDEES

Dawn Viveash, MD Sr. VP, Head, Global Quality, Regulatory Affairs and Safety
Teri Johnson, RAC Director, Regulatory Affairs and Development Strategic Planning
Preston Klassen, MD, MHS Sr. VP, Head of Development

1.0 BACKGROUND

The Division had serious concerns about Contrave's pressor effects, particularly in light of the results of SCOUT, and wanted the sponsor to present their interpretation of the blood pressure and pulse data to the Division. The sponsor presented this information on October 13, 2010 and followed up their submission on their CV proposal on November 3, 2010 via email. This TCON meeting was a follow-up correspondence on their CV proposal.

2. DISCUSSION

We informed the sponsor that we would like for them to submit a detailed design of an outcomes trial, which can include both approaches: randomized and observational. The sponsor indicated they will submit their outcomes proposal within 2-3 weeks but prior to the AC meeting on December 7, 2010.

Sponsor inquired about our thoughts on the REMS proposal that they submitted with the November 3, 2010 email. We informed the sponsor that no internal discussion has taken place but will correspond with them after it has.

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/s/

MEGHNA M JAIRATH
11/16/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: Contrave 200063_clinical question
Date: Thursday, November 04, 2010 1:39:31 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA

Attention: DMEP

5901-B Ammendale Road

Beltsville, MD 20705-1266

Respond by: November 8, 2010

Page 141 of your EMDAC briefing document states:

7.6.6 Renal Function

The special topic of renal function was addressed to further evaluate observations of a small increase in serum creatinine observed with NB treatment in the Phase 3 studies, as described

below. The likely reason for the creatinine increases is the finding that bupropion and its metabolites competitively inhibit the OCT2 in the basolateral membrane of the renal tubule

responsible for creatinine secretion.

1. Provide references for the underlined statement above.

Please confirm receipt of this email.

Meghna

Thanks.

Thanks
Eileen

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/s/

MEGHNA M JAIRATH
11/04/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_Clinical_11_03_10
Date: Wednesday, November 03, 2010 3:26:02 PM
Attachments: [11-03-2010 Contrave clin question.pdf](#)

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our Clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: November 8, 2010

Please see attachment.

Please confirm receipt of this email.

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)
[Center for Drug Evaluation and Research](#)
[Office of Drug Evaluation II](#)

Division of Metabolism & Endocrinology Products

Phone: 301-796-4267

Fax: 301-796-9712

Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
11/03/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: RE: NDA 200063_CMC_10_29_10
Date: Friday, October 29, 2010 2:37:44 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our CMC reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: November 2, 2010

1. Include in the Drug Product Specifications, as part of related Substances-Bupropion HCl, testing for the content of the potential genotoxic impurity (b) (4) with an acceptance criterion of NMT (b) (4) ppm.

2. Provide a validated analytical test method for the determination of (b) (4)

3. The limit of detection of method QUC-TM-00004, the analytical method employed for the determination of the potential genotoxic impurity (b) (4) is (b) (4) % (as given for "All others (specified and unspecified)") This limit of detection is not adequate to comply with the acceptance criterion of NMT (b) (4) ppm. Provide a validated test method capable of determining (b) (4) consistent with its acceptance criterion.

Please confirm receipt of this email.

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
10/29/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_stats_10_27_10
Date: Wednesday, October 27, 2010 1:49:26 PM
Attachments: [NDA200063CompletersRequest10-26-10.doc](#)

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our stats reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: October 29, 2010

Please see attached sheet.

Please confirm receipt of this email.

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)
[Center for Drug Evaluation and Research](#)

Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
10/27/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_clinical request_10_25_10
Date: Monday, October 25, 2010 1:42:00 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: October 27, 2010

ISE: page 67/438

3.3.3.7.3 Other Measures of Glycemic Control

Other secondary analyses conducted in NB-304 included the comparison between treatment groups in the proportion of subjects requiring rescue medications for diabetes, the proportion of subjects requiring changes in dose of oral hypoglycemic medications, and the proportion of subjects discontinuing study drug due to poor glycemic control. The proportion of subjects requiring rescue medications for glycemic control in the NB32 group was lower than placebo treatment (22.3% NB32 vs. 35.2% placebo). The odds ratio was 0.55 (95% confidence limit, 0.35 to 0.86) (Table 14.2-72 CSR NB-304). There were few subjects in each group with either dose reductions in oral hypoglycemic medication (1.9% NB32, 1.3% placebo) (Table 14.2-70 CSR NB-304), dose increases (3.0% NB32, 1.3% placebo) (Table 14.2-71 CSR NB-304), or who

discontinued investigational therapy due to poor glycemic control (0.0% NB32, 1.9% placebo) (Table 14.2-73 CSR NB-304).

Q1. In the subjects who required rescue medications for glycemic control, clarify if this refers to rescue medications for poor hyperglycemia control as opposed to hypoglycemia.

Please confirm receipt of this email.

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
10/25/2010



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: October 18, 2010
Meeting Location: Teleconference

Application Number: NDA 200063
Product Name: Contrave (naltrexone HCl/bupropion HCl) extended release tablets, 4 mg/90 mg and 8 mg/90 mg.
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss
Sponsor/Applicant Name: Orexigen Therapeutics, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

FDA ATTENDEES

Eric Colman, M.D. Deputy Director, Division of Metabolism and Endocrinology Products (DMEP)
Meghna M. Jairath, Pharm.D. Regulatory Project Manager, DMEP

SPONSOR ATTENDEES

Dawn Viveash, MD Sr.VP, Head, Global Quality, Regulatory Affairs and Safety
Teri Johnson, RAC Director, Regulatory Affairs and Development Strategic Planning

1.0 BACKGROUND

The Division has serious concerns about Contrave's pressor effects, particularly in light of the results of SCOUT, and wanted the sponsor to present their interpretation of the blood pressure and pulse data to the Division. The sponsor presented this information on October 13, 2010.

This TCON meeting was a follow-up correspondence.

2. DISCUSSION

We informed the sponsor that we would like for them to present a design of an outcomes trial. The sponsor indicated they will submit something to us shortly.

The sponsor also stated that they will be submitted an updated risk mitigation plan to us.

Both topics will be further discussed with us once we receive the information.

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/s/

MEGHNA M JAIRATH
10/21/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_ labeling request_10_5_10
Date: Tuesday, October 05, 2010 1:29:05 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our labeling reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: October 8, 2010

1. Indicate if you have conducted a usability study or a label comprehension study with the titration label on the container itself . If you have, then provide us with the results.

Please confirm receipt of this email.

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)
[Center for Drug Evaluation and Research](#)

Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
10/05/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: FW: NDA 200063_ clinical request_10_1_10
Date: Friday, October 01, 2010 4:35:50 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: October 6, 2010

Hello,

1. Submit outlier analysis results for PR and QRS intervals in diabetic patients.

Please confirm receipt of this email.

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)

Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
10/01/2010

From: [Teri Johnson](#)
To: [Jairath, Meghna;](#)
Subject: RE: NDA 200063_ clinical request_9_27_10
Date: Monday, September 27, 2010 2:54:07 PM

Good Morning/Afternoon Meghna –

A short note to acknowledge receipt and let you know that I'm preparing the list of attendees for the 13-Oct meeting and will send it to you momentarily.

I hope you had a great weekend,
Teri

From: Jairath, Meghna [mailto:Meghna.Jairath@fda.hhs.gov]
Sent: Monday, September 27, 2010 10:17 AM
To: Teri Johnson
Subject: NDA 200063_ clinical request_9_27_10

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: October 6, 2010

Please see attachment for our request.

Please confirm receipt of this email.

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
09/29/2010

From: Sharma, Khushboo
Sent: Thursday, September 23, 2010 4:20 PM
To: 'tjohnson@orexigen.com'
Subject: NDA 200-063

Dear Ms. Johnson,

Please refer to the letters of Authorization dated October 20, 2009 and December 17, 2009 in your submission that authorized us to review DMFs [REDACTED] ^{(b) (4)} in support of your NDA 200-063.

This is to notify you that we found these DMFs inadequate to support your supplement. A deficiency letter was sent to the respective DMF holders.

Please acknowledge the receipt of this email.

If you have any questions, please call me.

Thank you
Khushboo Sharma, MBA
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

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/s/

KHUSHBOO SHARMA
09/23/2010

From: Sharma, Khushboo
Sent: Tuesday, September 21, 2010 10:31 AM
To: 'tjohnson@orexigen.com'
Subject: NDA 200-063

Dear Ms. Johnson,

Please refer to the Letter of Authorization dated December 23, 2009 in your submission that authorized us to review DMF (b) (4) in support of your NDA 200-063.

This is to notify you that information has been requested from the (b) (4) for this DMF.

If you have any questions, please call me.

Thank you
Khushboo Sharma, MBA
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

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/s/

KHUSHBOO SHARMA
09/21/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_ request 17-Aug-10 Response
Date: Wednesday, September 01, 2010 11:18:32 AM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: September 8, 2010

Send the following request:

The patient-reported outcomes instruments, the Impact of Weight on Quality of Life (IWQOL-Lite) and the Control of Eating questionnaire (CoE) are intended to be used as evaluative measures to support claim of treatment benefit in obese patients. To date, the Agency has not received adequate evidence of the development and validation of the IWQOL-Lite and CoE to complete its review of the submission for Contrave according to principles set forth in the FDA's guidance for industry on Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims. We require you to submit more detailed materials for each instrument as indicated in the aforementioned guidance, including:

1. A copy of the instruments as completed by the patients (including

instructions to patients).

2. Investigators' and patients' study manual and/or training material and user manuals.

3. Documented evidence of the instruments' performance in the specific population in which it is used including but not limited to conceptual framework, content validity documentation, assessment of construct validity, reliability, and ability to detect change.

Please confirm receipt of this email.

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200063

ORIG-1

OREXIGEN
THERAPEUTICS
INC

CONTRAVE® (Naltrexone HCl
and Bupropion HCl)

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/s/

MEGHNA M JAIRATH

09/02/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_info request
Date: Thursday, September 02, 2010 2:30:22 PM

Hello,

1. Submit the population analysis data files as SAS transport files (*.xpt format) as you did during the original submission. Before submitting it to us, confirm that the xpt files match exactly with the csv files.

Thanks.

Meghna

From: Jairath, Meghna
Sent: Tuesday, August 24, 2010 9:58 AM
To: 'Teri Johnson'
Subject: NDA 200063_info request

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: 8/ 26 /10

1. We are unable to repeat the population PK and analysis using the data derived from SAS transport files submitted with the original submission (bupr.xpt, hydroxy.xpt, erythro.xpt, threo.xpt, nalt.xpt, beta.xpt, and nb303d.xpt). We also noted that the SAS transport files and the NONMEM output files submitted on 07/09/2010 differed in the analyte concentration values (Column Name=DV) indicating that the derived CSV files may be different than the original SAS datasets. Therefore, please provide us all the original, NONMEM analysis ready files used for population PK by the (b) (4) (bupropion.csv, hydroxy.csv, threo.csv, erythro.csv, naltrexone.csv, beta.csv, and nb303d.csv) as soon as possible. Also provide the csv format files used for PKPD analysis by (b) (4) (placebo.csv and weight3.csv).

Please respond with receipt.

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200063

ORIG-1

OREXIGEN
THERAPEUTICS
INC

CONTRAVE® (Naltrexone HCl
and Bupropion HCl)

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/s/

MEGHNA M JAIRATH

09/02/2010

From: [Teri Johnson](#)
To: [Jairath, Meghna](#);
Subject: RE: NDA 200063_info request
Date: Tuesday, August 24, 2010 11:10:40 AM

Good Morning Meghna –

Just a quick note acknowledging receipt. We will respond ASAP.

Best,
Teri

From: Jairath, Meghna [mailto:Meghna.Jairath@fda.hhs.gov]
Sent: Tuesday, August 24, 2010 6:58 AM
To: Teri Johnson
Subject: NDA 200063_info request

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266

Respond by: 8/ 26 /10

1. We are unable to repeat the population PK and analysis using the data derived from SAS transport files submitted with the original submission

(bupr.xpt, hydroxy.xpt, erythro.xpt, threo.xpt, nalt.xpt, beta.xpt, and nb303d.xpt). We also noted that the SAS transport files and the NONMEM output files submitted on 07/09/2010 differed in the analyte concentration values (Column Name=DV) indicating that the derived CSV files may be different than the original SAS datasets. Therefore, please provide us all the original, NONMEM analysis ready files used for population PK by the (b) (4) (bupropion.csv, hydroxy.csv, threo.csv, erythro.csv, naltrexone.csv, beta.csv, and nb303d.csv) as soon as possible. Also provide the csv format files used for PKPD analysis by (b) (4) (placebo.csv and weight3.csv).

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

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/s/

MEGHNA M JAIRATH
08/24/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_ request
Date: Tuesday, August 17, 2010 4:10:33 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by us. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: 8/18/10

1. This question is related to the utilizing a ^{(b) (4)} label which includes the dose escalation instructions: Does the label ^{(b) (4)}

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)

Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_ request
Date: Tuesday, August 17, 2010 4:10:33 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by us. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by: 8/18/10

1. This question is related to the utilizing a ^{(b) (4)} label which includes the dose escalation instructions: Does the label ^{(b) (4)}

Meghna

Thanks.

[Meghna M. Jairath, Pharm.D.](#)
[Regulatory Project Manager](#)
[Food & Drug Administration](#)

Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

Application
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/s/

MEGHNA M JAIRATH

08/18/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_clinical request
Date: Tuesday, August 17, 2010 11:49:02 AM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by : 8/20/10

Clinical

1. For Table 26 Jul2010-9.1. and Table ISS.P.BP.5-1:

Are the criteria for ≥ 2 or last post-baseline systolic blood pressure ≥ 140 (or 160) mm Hg and ≥ 2 or last post-baseline diastolic blood pressure ≥ 90 (or 100) mm Hg consecutive readings or any two readings?

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

Application
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/s/

MEGHNA M JAIRATH
08/17/2010



NDA 200063

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Orexigen Therapeutics, Inc.
3344 North Torrey Pines Road, Suite 200
La Jolla, California 92037

Attention: Dawn Viveash, MD.
Senior Vice President, Global Regulatory Affairs

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) dated March 31, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naltrexone Hydrochloride and Bupropion Hydrochloride Extended-release Tablets, 4 mg/90 mg and 8 mg/90 mg.

We also refer to your May 14, 2010, correspondence, received May 14, 2010, requesting review of your proposed proprietary name, Contrave. We have completed our review of the proposed proprietary name, Contrave and have concluded that it is acceptable.

The proposed proprietary name, Contrave, will be re-reviewed 90 days prior to the approval of the NDA.

If **any** of the proposed product characteristics as stated in your May 14, 2010, 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 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 Meghna Jairath at (301) 796-4267.

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

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Type/Number

Submitter Name

Product Name

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/s/

CAROL A HOLQUIST
08/04/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_clinical and clin pharm request
Date: Monday, July 26, 2010 8:43:48 AM
Attachments: [200063 clinical request 7-26-10.pdf](#)

NDA 200063

Dear Ms. Johnson:

The following information is being requested by us. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Respond by 8/02/10

Clinical

1. See PDF attachment for request.

Clinical Pharmacology

2. Provide justification for the use of Pharmacologically Weighted Composite (PAWC) metric in the exposure-response and other analyses, specifically in the context of proposed indication. Provide explanation on what pharmacological effect are these potency factors referring to for bupropion, naltrexone and their respective metabolites, and how these potency factors are relevant to the weight loss effect?

3. Provide specifically which literature is cited and/or listed drug is relevant to the question stated above

Meghna

Thanks.

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov

Application
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MEGHNA M JAIRATH
07/27/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: FW: NDA 200063_regulatory request
Date: Thursday, July 08, 2010 4:58:02 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by us. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Regulatory : Respond by 7/12/10

Hello,

1. Officially submit a copy of the proof of receipt of Paragraph 4 patent certification . If the recipient does/does not challenge after 45 days, let us know.
Thanks.

Meghna

Thanks.

*Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration*

*Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov*

Application
Type/Number

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Product Name

NDA-200063

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and Bupropion HCl)

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/s/

MEGHNA M JAIRATH
07/14/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: NDA 200063_OT_information request
Date: Thursday, July 08, 2010 2:31:20 PM
Attachments: [OT info request .pdf](#)

Hello,

See attached PDF document for OT information request.

Thanks.

Meghna

Application
Type/Number

Submission
Type/Number

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Product Name

NDA-200063

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/s/

MEGHNA M JAIRATH
07/13/2010



NDA 200063

FILING COMMUNICATION

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Sr. VP, Global Regulatory Affairs
3344 North Torrey Pines Rd. Suite 200
La, Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your new drug application (NDA) dated March 31, 2010, received March 31, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Contrave (naltrexone HCl/bupropion HCl) extended release tablets, 4 mg/90 mg and 8 mg/90 mg.

We also refer to your submission dated May 24, 2010 and reference telephone conversations on May 17, 19, and 21, 2010, between Meghna Jairath and Teri Johnson and May 21, 2010, between Enid Galliers of this Division and you in regards to the correct listed drugs for this 505(b)(2) application.

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 January 31, 2011.

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 January 10, 2011.

During our filing review of your application, we identified the following potential review issues:

Submit revised labeling that incorporates the following comments.

1. Under Highlights Overview Section:

- Add spaces between each major heading. (appears in WORD version only).
- ~~Delete~~ and Add: See 17 for PATIENT COUNSELING INFORMATION and (b) (4) Medication Guide. (appears in WORD version only)

2. Under Full Prescribing Information Table of Contents:

- The same title for the boxed warning that appears in the Highlights and Full Prescribing Information must also appear at the beginning of the Table of Contents in upper-case letters and bold type: Add, Warning: Suicidality and Antidepressant Drugs. (not added in both SPL and WORD versions).
- Delete all periods after the numbers of the section and subsection headings. (appears in SPL version only)
- Under section 17 Patient counseling Information:
 - ~~Delete~~ and Add: (b) (4) (appears in both SPL and WORD versions)
 - Since SPL R4 validation does not permit the inclusion of the Medication Guide as subsection under the Patient Counseling Information section, do not include the (b) (4) as a subsection heading. ~~Delete~~, (b) (4) (appears in both SPL and WORD versions)

3. Under Full Prescribing Information

- Delete all periods after the numbers of the section and subsection headings. (appears in both SPL and WORD versions).
- Some subheadings in WORD version are not bolded. Bold all subheadings.
- Under 17 Patient Counseling Information:
 - ~~Delete~~ and Add: “Patient information is printed at the end of this insert. (b) (4) this information and instructions provided in the (b) (4) Medication Guide should be discussed with patients.” (appears in both SPL and WORD versions)

- ~~Delete and Add:~~ [REDACTED] (b) (4) (appears in both SPL and WORD versions)
- ~~Delete :~~ [REDACTED] (b) (4) (appears in both SPL and WORD versions)
- ~~Delete:~~ [REDACTED] (b) (4) (appears in both SPL and WORD versions)

Clinical and Statistics

4. We request a full summary of the changes made to specific tables and figures in each document that took place as a result of the corrections to the efficacy endpoints in the clinical Study NB-303, in submission 0001 dated May 4, 2010.

Chemistry, Manufacturing and Controls

5. Your proposed commercial bupropion hydrochloride manufacturer [REDACTED] (b) (4) has two facilities with different street addresses. Clarify whether these two facilities are within a contiguous campus and summarize differences, if any, between them. If this is not the case, provide adequate CMC equivalence information to bridge the two facilities.

Clinical Pharmacology

6. Provide raw data (SAS transport files) and the model codes for the two Pharmacokinetic (PK) / pharmacodynamic(PD) studies (IR-PET and NB-222).
7. Provide the NONMEM and WINBUGS Model Codes for the PopPK and PopPK/PD analyses. You can follow the specifications mentioned in the Modeling and Simulations Plan Section 6 “Deliverables for Regulatory Submission” (page 325 of the Population Analysis Report by [REDACTED] (b) (4) Dated Feb 9, 2010). In general, model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps.

We are providing the above comments to give you preliminary notice of potential review issues. 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.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge that you have requested a (b) (4) of pediatric studies for this application. You have requested a (b) (4) and have checked the box entitled (b) (4). You state that (b) (4). This reason is not valid under PREA.

Accordingly, a (b) (4) for pediatric studies for this application is denied at this time. Within 30 days of the date of this letter, please submit your pediatric plan outlining the pediatric studies that you plan to conduct to meet the PREA requirements. The plan should address whether and, if so, under what grounds, you plan to request a partial waiver or deferral of pediatric studies. Please note that if you request a partial waiver, your request must be for one of the reasons stated in the law. You must also provide justification as to why you believe this product qualifies for such a waiver.

The pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/ pharmacodynamics, safety, efficacy) sufficient to demonstrate dose, safety, and efficacy. The plan should address all relevant pediatric subpopulations. The pediatric plan must contain a timeline for the completion of pediatric studies, i.e. the dates of (1) protocol submission, (2) study completion and (3) submission of study reports. In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. (See Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>).

If you have any questions, call Meghna M. Jairath, Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

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

Application
Type/Number

Submission
Type/Number

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/s/

ERIC C COLMAN
06/11/2010

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our clinical reviewer. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Clinical: Respond by June 7, 2010

Our medical reviewer is requesting additional Adverse Event analysis and/or clarification for areas of special interest.

Question 1. Requesting an analysis for renal and hepatic events using a different collection of Preferred Terms than presented by Orexigen in the ISS.

Preferred Terms to be Searched for Renal Adverse Events of Special Interest

Preferred Terms for Renal Events

Acute prerenal failure
Anuria
Azotaemia
Dialysis
Haemodialysis
Hepatorenal failure
Hepatorenal syndrome
Nephropathy toxic
Oliguria
Postrenal failure
Renal failure acute
Renal failure
Renal impairment
Renal tubular necrosis
Nephritis interstitial
Glomerulonephritis
Blood creatinine increased
Blood creatinine abnormal
Creatinine renal clearance decreased
Renal failure chronic
Blood urea abnormal
Blood urea increased
Renal function test abnormal
Glomerular filtration rate decreased
Glomerular filtration rate abnormal
Urine albumin/creatinine ratio increased
Urine albumin/creatinine ratio abnormal
Urine protein/creatinine ratio increased
Urine protein/creatinine ratio abnormal

Preferred Terms to be Searched for Hepatic Adverse Events of Special Interest

Ascites	Jaundice
Asterixis	Jaundice cholestatic
Biliary cirrhosis	Jaundice hepatocellular
Biliary cirrhosis primary	Liver transplant
Biliary fibrosis	Ocular icterus
Hepatic cirrhosis	Yellow skin
Coma hepatic	Alanine aminotransferase increased
Cryptogenic cirrhosis	Alanine aminotransferase abnormal
Cytolytic hepatitis	Aspartate aminotransferase increased
Hepatic calcification	Aspartate aminotransferase abnormal
Hepatic encephalopathy	Blood bilirubin increased
Hepatic failure	Blood bilirubin abnormal
Hepatic infiltration eosinophilic	Bilirubin conjugated increased
Hepatic necrosis	Blood bilirubin unconjugated increased
Hepatic steatosis	Hepatic enzyme abnormal
Hepatitis	Hepatic enzyme increased
Hepatitis acute	Liver function test abnormal
Hepatitis cholestatic	Liver disorder
Hepatitis fulminant	Gamma-glutamyltransferase increased
Hepatitis toxic	Gamma-glutamyltransferase abnormal
Hepatobiliary disease	Hepatic function abnormal
Hepatorenal failure	Granulomatous liver disease
Hepatorenal syndrome	Transaminase increased
Hepatotoxicity	Transaminases abnormal
Hyperammonaemia	

RENAL:

Please generate the following tables using the list of preferred terms for renal events:

**Table: Summary of Subjects with Treatment-Emergent Adverse Events of Special Interest:
Renal Events (Primary Dataset, Double-Blind Treatment Phase)**

MedDRA preferred term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Total of Renal Events				
D/C overall due to renal events				
Blood creatinine increased*				
Discontinuations				
Blood urea increased				
Discontinuations				
Creatinine renal clearance decreased				
Discontinuations				
Renal failure				
Discontinuations				
Renal failure acute				
Discontinuations				
Renal failure chronic				
Discontinuations				
Renal impairment				
Discontinuations				

* only list preferred terms from the list that have an event—if there are no events in either placebo, NB 16 or NB 32 then do not list it

Table Summary of Subjects with Treatment-Emergent Adverse Events of Special Interest: Renal Events, Changes in Laboratory Tests (Primary Dataset, Double-Blind Treatment Phase)

	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Renal Events – Changes in Laboratory Tests^a				
Led to discontinuation				
Met creatinine criterion ^b				

a. The following preferred terms are included in the definition of this category: blood creatinine increased, blood creatinine abnormal, renal function test abnormal, creatinine renal clearance decreased, glomerular filtration rate decreased, and glomerular filtration rate abnormal

b. Creatinine post-baseline value > 2 mg/dL or ≥ 100% increase from baseline value.

Table Number of Subjects Meeting Criteria After Baseline for Creatinine Values of Special Interest (Primary Dataset, Double-Blind Treatment Phase)

	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Creatinine (mg/dL) – Changes in Laboratory Tests^a				
≥ 50% increase from baseline and > ULN on single occasion				
≥ 100% increase from baseline				
> 2 mg/dL				

a. To meet criteria for laboratory values of special interest, value has to be more extreme than the baseline value.

Diabetic vs Non-diabetic datasets:

Table: Summary of Subjects with Treatment-Emergent Adverse Events of Special Interest: Renal Events (Diabetic and Non-diabetic Dataset, Double-Blind Treatment Phase)

	Non-diabetic dataset		Diabetic dataset	
MedDRA preferred term	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB 32 (N=333) n (%)
Total of Renal Events				
D/C overall due to renal events				
Blood creatinine increased*				
Discontinuations				
Blood urea increased				
Discontinuations				
Creatinine renal clearance decreased				
Discontinuations				
Renal failure				
Discontinuations				
Renal failure acute				
Discontinuations				
Renal failure chronic				
Discontinuations				
Renal impairment				
Discontinuations				

* only list preferred terms from the list that have an event—if there are no events in either placebo, NB 16 or NB 32 then do not list it

Table Summary of Subjects with Treatment-Emergent Adverse Events of Special Interest: Renal Events, Changes in Laboratory Tests (Diabetic and Non-diabetic Dataset, Double-Blind Treatment Phase)

	Non-diabetic dataset		Diabetic dataset	
	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB 32 (N=333) n (%)
Renal Events – Changes in Laboratory Tests^a				
Led to discontinuation				
Met creatinine criterion ^b				

a. The following preferred terms are included in the definition of this category: blood creatinine increased, blood creatinine abnormal, renal function test abnormal, creatinine renal clearance decreased, glomerular filtration rate decreased, and glomerular filtration rate abnormal

b. Creatinine post-baseline value > 2 mg/dL or ≥ 100% increase from baseline value.

Table Number of Subjects Meeting Criteria After Baseline for Creatinine Values of Special Interest (Diabetic and Non-diabetic Dataset, Double-Blind Treatment Phase)

	Non-diabetic dataset		Diabetic dataset	
	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB 32 (N=333) n (%)
Creatinine (mg/dL) – Changes in Laboratory Tests^a				
≥ 50% increase from baseline and > ULN on single occasion				
≥ 100% increase from baseline				
> 2 mg/dL				

a. To meet criteria for laboratory values of special interest, value has to be more extreme than the baseline value.

HEPATIC:

Please generate the following tables using the list of preferred terms for hepatic events:

Table. Summary of Subjects with Treatment-Emergent Adverse Events of Special Interest: Hepatic Events (Primary Dataset, Double-Blind Treatment Phase)

MedDRA preferred term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Total of Hepatic Events				
D/C overall due to hepatic events				
ALT increase *				
Discontinuations				
AST increased				
Discontinuations				
Blood bilirubin increased				
Discontinuations				
Hepatic enzyme increased				
Discontinuations				
Hepatic function abnormal				
Discontinuations				
Jaundice				
Discontinuations				
Liver function test abnormal				
Discontinuations				

* only list preferred terms that have an event—if there are no events in either placebo, NB 16 or NB 32 then do not list it

Table. Summary of Subjects with Treatment-Emergent Adverse Events of Special Interest: Hepatic Events, Changes in Laboratory Tests (Primary Dataset, Double-Blind Treatment Phase)

	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Hepatic Events – Changes in Laboratory Tests^a				
Led to discontinuation				
Met ALT or AST criteria ^b				

a. The following preferred terms are included in the definition of this category: ALT increased, ALT abnormal, AST increased, AST abnormal, transaminases increased, transaminases abnormal, hepatic enzyme increased, hepatic enzyme abnormal, liver function test abnormal, blood bilirubin increased, blood bilirubin abnormal, bilirubin conjugated increased, and blood bilirubin unconjugated increased.

b. ALT or AST post-baseline value > 3 x ULN on 2 consecutive visits or 5 x ULN on any occasion

Table. Number of Subjects Meeting Criteria After Baseline for ALT/AST Values of Special Interest (Primary Dataset, Double-Blind Treatment Phase)

Laboratory Parameter Criteria^a	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
ALT > 3x ULN on 2 consecutive occasions				
ALT > 5x ULN on single occasion				
AST > 3x ULN on 2 consecutive occasions				
AST > 5x ULN on single occasion				

a. To meet criteria for laboratory values of special interest, value had to be more extreme than the baseline value.

Question 2:

Hypertension terms in Orexigen’s Hypertension subtopic using MedDRA 12.0:

- Blood pressure systolic increased
- Blood pressure diastolic increased
- Blood pressure increased
- Hypertension
- Labile hypertension
- ECG signs of ventricular hypertrophy
- Cardiovascular disorder

Please confirm that either (1) there are no cases in the database for the Preferred Terms listed below or (2) if these terms are present in the database then please submit an updated Table 2-56 (found on page 149 of the ISS) to include this information.

- Blood pressure orthostatic increased
- Accelerated hypertension
- Blood pressure ambulatory increased
- Diastolic hypertension
- Essential hypertension
- Hypertensive crisis
- Hypertensive emergency
- Malignant hypertension
- Orthostatic hypertension
- Prehypertension
- Systolic hypertension

Question 3:

Preferred Terms in Orexigen’s Atherosclerotic Disease subtopic using MedDRA 12.0:

Subtopic: Atherosclerotic Disease
Category: Major CV

Preferred Terms: Myocardial infarction, cerebrovascular accident

Please confirm that either (1) there are no cases in the database for the following Preferred Terms or (2) If these terms are present in the database then please submit an updated Table 2-60 (found on page 159 of the ISS) to include this information.

Acute coronary syndrome, Acute myocardial infarction, Blood creatine phosphokinase MB increased, Silent myocardial infarction, Infarction; Ischaemic cerebrovascular conditions (SMQ)

Question 4:

Preferred Terms in Orexigen's Atherosclerotic Disease subtopic using MedDRA 12.0:

Subtopic: Atherosclerotic Disease

Category: Angina

Preferred Terms: Angina pectoris, angiopathy, coronary artery disease, coronary artery occlusion, troponin increased,

Please confirm that either (1) there are no cases in the database for the following Preferred Terms or (2) If these terms are present in the database then please submit an updated Table 2-60 (found on page 159 of the ISS) to include this information.

Coronary artery thrombosis, Troponin I increased, Troponin T increased, Blood creatine phosphokinase MB increased, Blood creatine phosphokinase increased, Cardiac enzymes increased, Angina unstable, Arteriosclerosis coronary artery, Coronary angioplasty, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery stenosis, ECG signs of myocardial ischaemia, Ischaemic cardiomyopathy, Myocardial ischaemia, Cardiac stress test abnormal

Thanks.

*Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200063	ORIG-1	OREXIGEN THERAPEUTICS INC	CONTRAVE® (Naltrexone HCl and Bupropion HCl)

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/s/

MEGHNA M JAIRATH
06/08/2010

From: [Jairath, Meghna](#)
To: ["Teri Johnson";](#)
Subject: FW: NDA 200063_clinical and CMC request
Date: Wednesday, May 19, 2010 2:25:04 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by us. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Regulatory Clinical: Respond by 5/20/10

Hello,

1. Provide an updated cover letter and 356h form with the correct listed products.
2. Provide the missing unexpired patent information for Aplenzin and Wellbutrin XL.
3. Provide a comprehensive index.
4. Provide a comprehensive table of what listed product is referenced for literature, safety, efficacy, etc.,
5. Provide a more legible package insert copy for Revia and Vivitrol. Also provide the current package insert for Wellbutrin and Wellbutrin XL that you have noted as listed products. All the package insert should be easily accessible.

Thanks.

[Meghna M. Jairath, Pharm.D.](#)

*Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov*

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200063

ORIG-1

OREXIGEN
THERAPEUTICS
INC

CONTRAVE® (Naltrexone HCl
and Bupropion HCl)

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/s/

MEGHNA M JAIRATH
05/20/2010

From: [Tran, Suong T](#)
To: [Henry, Don](#); [Jairath, Meghna](#);
cc: [Galliers, Enid M](#); [Peri, Prasad](#);
Subject: EER please FW: NDA200063 from OREXIGEN drug name
Date: Tuesday, April 06, 2010 9:09:20 AM

Hi Don!

Please create an EER for this new NDA to send the manufacturing/testing facilities to Compliance. The info is in Form 356h, all facilities are ready for inspection.

Hi Meghna!

Please ask the applicant to confirm that all the manufacturing/testing facilities listed in Form 356h are ready for GMP inspections - this info is required for filing.

Thanks!

Su

-----Original Message-----

From: Galliers, Enid M
Sent: Monday, April 05, 2010 10:45 PM
To: Jairath, Meghna; Tran, Suong T
Cc: Madara, Patricia
Subject: FW: NDA200063 from OREXIGEN drug name

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

-----Original Message-----

From: EDRAdmin@fda.hhs.gov [<mailto:EDRAdmin@fda.hhs.gov>]
Sent: Monday, April 05, 2010 5:33 PM
To: Craig, Eileen; Galliers, Enid M; Derr, Janice; Khurana, Manoj; Brundage, Patricia; Madara, Patricia; Worrell, Sallamar; Huang, Zei Pao; CDER-OND-DMEP-EDRNOTIFY; CDER-EDRADMIN

Cc: CDER-EDRSTAFF
Subject: NDA200063 from OREXIGEN drug name

Hi!

The EDR has received an Electronic Document on for division 510:
If you have received this in error please contact your Project Manager.

NDA# N200063
Incoming Document Type: N
Incoming Document Type Sequence Number: 1
Supplement Modification Type:
Letter Date: 31-MAR-2010

It has sections 1, 2, 3, 4, 5
The network location is : \\CDSESUB1\EVSPROD\NDA200063\200063.ENX
It is now available on the network. You can review this submission by entering
EDR in your browser.

If you have any problem accessing this submission contact:

EDRAdmin@fda.hhs.gov

Thanks,
PE

From: [Craig, Eileen](#)
To: [Jairath, Meghna](#);
[Madara, Patricia](#);
Subject: NDA 200-063 (Contrave) questions
Date: Tuesday, April 13, 2010 12:35:37 PM

Hi Meghna

I am trying to find information in the submission regarding the investigators and # of subjects screened, randomized etc but have been unable to do so. Can you please request the following information from Orexigen, (to be submitted within 2 weeks)? If Orexigen believes that the information has already been submitted, please specify where in the NDA application it can be found.

1. How many study subjects did Dr Steven Smith enroll and in which study?
2. How many study subjects did Dr Mark Graves enroll and in which study?
3. Please provide the following information for all of the four Phase 3 studies [NB-301 (34 sites in the US), NB-302 (9 sites in the US), NB 303 (36 sites in the US), and NB-304 (53 sites in the US)] for the 5 Principal Investigators or Subinvestigators who randomized the most subjects in each Phase 3 study. There should be 5 investigators for each study for a total of 20 investigators.

Investigator (Site #, Study#) Treatment	# Subjects Randomized	# Subjects Treated	# Subjects Discontinued	% of Randomized Subjects that Discontinued
All Sites				
Study Trt A				
Study Trt B				
Placebo				
Total				
Doe, John (123, Study AB)				
Study Trt A				
Study Trt B				
Placebo				
Total				

From: [Jairath, Meghna](#)
To: "[Teri Johnson](#)";
Subject: NDA 200063_clinical and CMC request
Date: Tuesday, April 13, 2010 1:31:36 PM

NDA 200063

Dear Ms. Johnson:

The following information is being requested by our clinical and CMC reviewers. We would like you to provide the information described below. The information must be submitted officially to your NDA 200063 at the Beltsville address shown below. If you wish to make the information available to the reviewer more quickly, you may email it in addition.

Please note that ALL regulatory submissions must be sent to the following address:

**CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266**

Clinical: Respond by 4/26/10

Hello,

We are unable to locate the following information that we are requesting. If you believe that the information has already been submitted, please specify where in the NDA application it can be found.

1. How many study subjects did Dr Steven Smith enroll and in which study?
2. How many study subjects did Dr Mark Graves enroll and in which study?
3. Provide the following information for all of the four Phase 3 studies [NB-301 (34 sites in the US), NB-302 (9 sites in the US), NB 303 (36 sites in the US), and NB-304 (53 sites in the US)] for the 5 Principal Investigators or Subinvestigators who randomized the most subjects in each Phase 3 study. There should be 5 investigators for each study for a total of 20 investigators.

Investigator (Site #, Study#)	# Subjects Randomized	# Subjects Treated	# Subjects Discontinued	% of Randomized Subjects that Discontinued
Treatment				
All Sites				
Study Trt A				
Study Trt B				
Placebo				
Total				
Doe, John (123, Study AB)				
Study Trt A				
Study Trt B				
Placebo				

Total				

CMC: Respond by 4/26/10

1. Please confirm that all the manufacturing/testing facilities listed in Form 356h are ready for GMP inspections
- this info is required for filing.

Thanks.

*Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Food & Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism & Endocrinology Products
Phone: 301-796-4267
Fax: 301-796-9712
Meghna.Jairath@fda.hhs.gov*

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200063

ORIG-1

OREXIGEN
THERAPEUTICS
INC

CONTRAVE® (Naltrexone HCl
and Bupropion HCl)

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/s/

MEGHNA M JAIRATH
04/14/2010



NDA 200063

NDA ACKNOWLEDGMENT

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Sr. VP, Global Regulatory Affairs
3344 North Torrey Pines Rd. Suite 200
La, Jolla, CA 92037

Dear Dr. Viveash:

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: Contrave (naltrexone HCL 4mg and 8mg /bupropion HCL 90mg)
extended release tablets

Date of Application: March 31, 2010

Date of Receipt: March 31, 2010

Our Reference Number: NDA 200063

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 May 30, 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 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, please call me at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, 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-200063

ORIG-1

OREXIGEN
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/s/

MEGHNA M JAIRATH
04/12/2010

11-7-2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,858

Orexigen Therapeutics, Inc.
Attention: Eduardo Dunayevich, M.D.
Chief Medical Officer
12481 High Bluff Drive; Suite 150
San Diego, CA 92130

Dear Dr. Dunayevich:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone/bupropion).

We also refer to the meeting between representatives of your firm and the FDA on October 1, 2007. The purpose of the meeting was to discuss your phase 3 development program for Contrave.

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}

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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 1, 2007
TIME: 1:00 PM Eastern time
LOCATION: Building 22; White Oak Campus
APPLICATION: IND 68,858
DRUG NAME: Contrave (naltrexone/bupropion)
TYPE OF MEETING: Type B; End of Phase 2

MEETING CHAIR: Eric Colman, M.D.; Deputy Director, DMEP

MEETING RECORDER: Pat Madara

FDA ATTENDEES:

Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Eileen Craig, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader
Fred K. Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Pat Madara, M.S.	Regulatory Project Manager

Office of Biometrics; Division of Biostatistics II

Todd Sahlroot, Ph.D.	Deputy Director
Janice Derr, Ph.D.	Biometrics Reviewer

Office of Biometrics; Division of Biostatistics VI

Yu-Te Wu, Ph.D.	Biometrics Reviewer
George Rochester, Ph.D.	Biometrics Team Leader

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Sally Choe, Ph.D.	Clinical Pharmacology Team Leader
Manoj Khurana, Ph.D.	Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment; Division of Pre-Marketing Assessment I

Suong Tran, Ph.D.	Pharmaceutical Assessment Lead, Branch 2

Office of the Director; Controlled Substance Staff

Patricia Beaston, M.D., Ph.D.	Medical Officer
Silvia Calderon, Ph.D.	Team Leader, CSS

EXTERNAL CONSTITUENT ATTENDEES:

Orexigen Therapeutics, Inc

Gary Tollefson, M.D., Ph.D.
Eduardo Dunayevich, M.D.
Anthony McKinney

CEO and President
Chief Medical Officer
Chief Operating Officer

(b) (4)

Ron Landbloom, M.D.
Janelle Erickson, Ph.D

Regulatory and Clinical Development
Principal Statistician

(b) (4)

Background:

IND 68,858 (Contrave; naltrexone/bupropion) is a fixed dose combination oral tablet being developed for the treatment of obesity. On June 29, 2007, Orexigen Therapeutics, Inc. submitted a Type B meeting request for an End-of-Phase 2 meeting. The focus of the meeting was to discuss specific issues related to the Phase 3 development plans for Contrave.

Pre-meeting draft responses to specific questions were sent to the sponsor on September 28, 2007. Based on this information, the sponsor determined that no further discussion of questions #1, 3, 4, 6, 7, and 9 was required. Therefore, these questions and responses are not included in this document.

Questions and Answers

Note: only comments made by Orexigen at the meeting are in *italics* and only comments made by FDA at the meeting are in **Bold** font.

Question 1:

No further discussion required.

Question 2:

Reference is made to Serial No. 0047 in which Orexigen indicates that equivalence has been demonstrated between the 8/90 trilayer tablets manufactured with bupropion HCl (b) (4) through an established IVIVC (b) (4) was also presented in Serial No. 0047 based on the information provided. Clinical trial materials manufactured at both of the sites for the bupropion HCl (b) (4) are being used for use in Clinical Trials NB-302 and NB-304.

Can the Agency confirm that the established IVIVC and other information provided in Serial No. 0047 are sufficient to support the (b) (4)

DMEP Response:

No. The abbreviated report on IVIVC submitted in Serial No. 0047 did not provide us with sufficient information to accept the claim that you have an established IVIVC (b) (4)

The Agency sees a potential issue in using (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
and the Agency recommends that you submit your detailed report and relevant data if you would like to claim for an established IVIVC.

Additional Sponsor Comments

The sponsor clarified that Clinical Studies NB-302 and NB-304 used tablets manufactured with the (b) (4) (b) (4)

Neither manufacturer will produce the (b) (4) for the commercial product.

The commercial manufacturer of this component is (b) (4) and the commercial tablet made by (b) (4) will be used in the phase 3 trials. Tablets manufactured with the (b) (4) from the 3 manufacturers were used in the Bioequivalence study NB-228.

The sponsor commented that only a small number of patients from the phase 3 trials would be treated with tablets manufactured with the (b) (4)

Additional DMEP Comment

Submission serial #047 did not (b) (4) help us review and agree to your claim of an established IVIVC. A bioequivalence study is required if the formulation for pivotal phase 3 studies is different from the to-be-marketed formulation.

Based on what we have heard today, it seems that the current products made with (b) (4) from (b) (4) are the major formulations that would be used in your phase 3 studies. Your request for a (b) (4) comparing the earlier products made with (b) (4) might not be necessary provided that the current products made with (b) (4) from (b) (4) and (b) (4) are bioequivalent.

Questions 3a, 3b and 4:

No further discussion.

Question 5:

Orexigen believes the approved bupropion drug product label and provided reference reflects a full characterization of CYP450s metabolism for this drug. Therefore assessment of the potential for a drug-drug interaction between bupropion and naltrexone can be assessed by supplementing CYP450 data for naltrexone. The proposed study design will address the potential for a drug-drug interaction with particular emphasis on CYP2B6 and CYP2D6.

1. Induction in Hepatocytes

Human hepatocytes (freshly plated or plateable cryopreserved) will be used to determine the potential for CYP isoform induction.

- Number of donors: 3 human donors
- Enzymes: CYP1A2, CYP2B6, CYP3A4 and CYP2D6
- Test compound concentrations: 3 concentrations
- Replicates: N = 3 for experimental group; N = 4 for positive and vehicle control groups; N = 2 for test article interference control group
- Analysis: Induction potential measured by enzymatic activity

2. Inhibition in Liver Microsomes

Human liver microsomes and CYP-specific substrates will be used to determine the potential for CYP isoform inhibition. IC₅₀ values will be calculated, where applicable.

- Enzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, AND CYP3A4
- CYP substrates: phenacetin (CYP1A2); coumarin (CYP2A6); S-mephenytoin (CYP2B6); paclitaxel (CYP2C8); tolbutamide (CYP2C9); S-mephenytoin (CYP2C19); dextromethorphan (CYP2D6); chlorzoxazone (CYP2E1); testosterone and midazolam (CYP3A4)
- Test compound concentrations: 5 concentrations
- Replicates: N = 3 for experimental group; N = 4 for positive and vehicle control groups; N = 2 for test article interference control group
- Analysis: Inhibition potential measured by enzymatic activity.

Does the Agency agree that this plan is sufficient to assess the potential effects of Naltrexone on the metabolism of other drugs? Moreover, does the Agency agree that no additional testing is needed on the bupropion potential for drug-drug interactions?

DMEP Response:

Yes, your plan seems sufficient to assess the potential effects of naltrexone on the metabolism of other drugs. However, if you see significant effects in your *in vitro* studies, additional *in vivo* drug-drug interaction studies may be warranted.

We also recommend that in your development program you should consider evaluation of interaction between the naltrexone-bupropion combination (NB) and representative anti-hypertensive, anti-diabetic drugs and lipid lowering drugs, which may be used concurrently in the target patient population.

Additional Sponsor Comment

The sponsor had felt that in vitro studies would be adequate. Orexigen asked how representative drugs should be selected – what criteria should be used.

Additional DMEP Comments

It is very likely that the target patient population for your drug will already be taking

multiple other drugs from different classes. While our suggestions are not specific to a particular drug to study, you need to establish the safety profile of your product in patients when these other drugs are co-administered. The agents that you may consider for your drug-drug interaction studies include representative compounds from the following categories:

Anti-hypertensives, including

- **Ace inhibitors**
- **Beta blockers**
- **Calcium channel blockers**
- **Angiotensin receptor blockers (ARBs)**

Lipid lowering drugs such as atorvastatin

Antidiabetic drugs such as metformin and/or sulfonylureas

A single dose drug-drug interaction (DDI) study is probably sufficient for conducting the DDI studies. While the Agency prefers a typical clinical pharmacology phase 1 DDI study, conducting the DDI analysis within you phase 3 studies might be possible. However, you should keep in mind that this approach may be challenging due to potential confounding factors.

Questions 6 and 7:

No further discussion required.

Question 8:

Orexigen believes that the previously presented NB-201 results and the phase III plan described in this document and appendices should provide sufficient data in support of an NDA filing for the Naltrexone-Bupropion combination product (Contrave™) for the treatment of obesity.

Does the Agency concur that the proposed phase III studies appear to be adequately designed and the total number of patient exposures appear sufficient to support an NDA filing for treatment of obesity?

DMEP Response:

Clinical Comments:

- You estimate 1500 one-year non-titration exposures to the naltrexone-bupropion combination (NB) and 700-750 one-year exposures to placebo from randomized, double-blind studies. These patient exposures appear sufficient to support NDA filing for the treatment of obesity.

However, after revisiting the question of whether the data from NB-201 satisfy the requirements for a fixed-dose combination product, we believe that additional data comparing the individual components to the combination product should be obtained to

confirm the results observed in NB-201. See our response to question 15 for additional details.

- The Inclusion Criteria in Phase III studies should have TSH within the upper limits of normal rather than (b) (4)ULN.

Safety Analysis Comments:

- All safety data should be submitted in CDISC format. Analysis data sets to support specific safety analyses should follow the principles in the Analysis Data Model (ADaM). It is advisable that you consult with the reviewing division if further clarification is needed.
- As stated at Page 2 of the statistical analysis plan (appendix IV), the safety analysis set will include all randomized subjects who are administered at least one tablet of study treatments. The safety analysis population should include all randomized subjects who take at least one dose of study treatment and have at least one investigator contact/assessment at any time after the start of study treatment, regardless of whether or not they discontinue the study.
- Regarding the summaries of treatment-emergent AEs and serious AEs, in addition to the summaries by the primary system organ class (SOC) terms as proposed in the SAP, evaluations by all levels of the MedDRA hierarchy (high level terms, high level group terms) are necessary so that similar events that may represent the same safety risk can be properly grouped. The primary SOC for a preferred term is the primary analysis. In addition, alternative summaries of all secondary SOCs should be provided. For such analysis, if one event maps to multiple secondary SOCs, each of those secondary SOCs should be represented.
- Certain Adverse Events of Special Interest (AESIs) should be identified and those with higher incidence rates associated with the use of Naltrexone and Bupropion should be summarized. In addition to the preferred terms listed at the page 6, other events should be considered, including seizures, joint and muscle pains. Exploratory analyses using Kaplan-Meier analyses should be provided. For all important adverse events it is recommended that the Case Report Forms be provided with the NDA submission.
- When multiple laboratory/vital sign/ECG results exist for a post-baseline time point, the analysis of maximum change from baseline should be provided in the summary table in addition to the first non-missing result as proposed. If multiple laboratory/vital sign/ECG results exist for the baseline time point, please discuss how the baseline measurement is defined. Refer to the CDISC ADaM Model for Change from Baseline Analyses. Please provide analysis datasets to support your summaries.

Clinical Pharmacology Comments:

- From a clinical pharmacology perspective, it is not clear whether you have sufficient information on systemic exposure of naltrexone/bupropion and their active/inactive metabolites in obese subjects. We therefore strongly recommend that you measure drug exposure (naltrexone, bupropion, and their metabolites) in future clinical trials (e.g. proposed Phase 3 trials NB-301 and NB-303) using an appropriate population PK sampling

strategy. These exposure data will be useful in establishing population PK and/or exposure-response relationship in the obese population.

- We also encourage you to refer to the following Guidance documents:
 - a. *Guidance for Industry-Population Pharmacokinetics, and*
 - b. *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications.*

Additional Sponsor Comments:

^{(b) (4)}ULN was used as the TSH upper limit for inclusion in previous studies, it is unclear why phase 3 studies should be modified to stipulate TSH levels within the upper limits of normal.

The sponsor asked for information regarding the appropriate sampling strategy to obtain additional systemic data in the phase 3 studies (sample size and endpoints of interest).

Additional DMEP Comments:

The Inclusion Criteria in Phase III studies should have TSH within the upper limits of normal. Studies that have already started may use the ^{(b) (4)}ULN cut-off.

You do not have sufficient PK information in obese subjects so it is important to capture exposure data in your future trials. Also, we cannot determine the PK profile of your drug product, because you submitted only the published literature data. The exposure – response relationship also needs to be understood for your combination product in the obese population.

The data for population analysis can be collected in a meaningful subpopulation during your ongoing and future trials.

Question 9:

No further discussion required.

Question 10:

The inferential tests associated with the key secondary endpoints will be performed in accordance with the Closed Testing Procedure (CTP) principle to prevent inflation of the family-wise type 1 error rate due to hypothesis testing of multiple secondary endpoints.

The CTP will be structured as follows: If the null hypothesis for the co-primary analysis of the co-primary efficacy endpoint are rejected at the two-sided 0.05 level of significance then testing of the secondary efficacy endpoints will proceed in a sequential step-down manner. Testing of each secondary endpoint in order will continue provided the null hypothesis for the previously tested secondary endpoint is rejected at the two-sided significance level of 0.05. Otherwise, no further testing will be done.

The list and ordering of secondary endpoints that Orexigen proposes be considered for labeling are listed in Appendix 4. Orexigen has provided a summary background information on the Mood, Quality of Life and Food Craving scales proposed for (b) (4)

Orexigen believes that positive results of the proposed secondary endpoint analyses would support their (b) (4)

Does the Agency agree with the proposed secondary endpoints? Moreover, does the Agency agree that, if the secondary measures proposed demonstrate statistically significant differences between active and placebo treatment, those findings could be (b) (4) ?

DMEP Response:

Endpoints that include measures of quality-of-life from validated instruments, blood pressure, pulse, lipoprotein lipids, fasting glucose and insulin, HbA1c in type 2 diabetics and waist circumference are appropriate secondary endpoints and would be considered for (b) (4) at the time of NDA review. We concur with the proposed protocol for testing the secondary efficacy endpoints in a sequential step-down manner, conditional on the statistical significance of both co-primary efficacy endpoints. However, it is important to recognize that even though secondary variables are pre-specified and the overall type I error rate is controlled for, that does not necessarily guarantee that all secondary variables will be (b) (4) if the differences between product and placebo groups are of nominal statistical significance. The clinical significance and consistency across studies of any observed differences will be important in determining whether secondary efficacy data merit inclusion in the (b) (4). As clinical significance is open to interpretation for many of these secondary outcome variables, determination of their meaningfulness would be made at the time of the NDA review.

Whether the Food Craving scale and the endpoint change in hs-CRP would be (b) (4) is a review issue. Detailed information in support of the reliability and validity of the Patient Reported Outcome (PRO) instrument used to measure food craving should be provided to support this endpoint. DMEP will consult with the Study Endpoints and Label Development (SEALD) team for an evaluation of this information. The SEALD team evaluates PRO instruments used to support effectiveness endpoints in clinical studies. As stated in the draft Guidance, the Agency generally intends to review a PRO instrument for: reliability, validity, ability to detect change, and interpretability. To facilitate this review, we recommend that you include the PRO instrument, instructions to the patient and a description of how the recorded information will be used to construct this secondary food craving endpoint. In addition, provide information in support of the reliability and validity of the PRO instrument (see the draft Guidance for additional information concerning the review of PRO instruments).

Additional Sponsor Comments:

The sponsor noted that they are hoping for a (b) (4). In fact, they are hoping for improvement.

Additional DMEP Comments:

If there is a demonstrated benefit, it may be possible to include that in the label but it would be a review issue.

Regarding your food cravings inventory (FCI) instrument, you should submit it and all relevant background and validation information to your IND. It will then be consulted to the SEALD team.

Question 11:

Orexigen proposes that the results of Study NB-304, (A Multicenter, Randomized, Double Blind, Placebo Controlled Study Comparing the Safety and Efficacy of Naltrexone 32 mg Sustained Release (SR)/Bupropion 360 mg Sustained Release (SR) and Placebo in Obese Subjects with Type 2 Diabetes Mellitus) may also be (b) (4)

Does the Agency agree?

DMEP Response:

While this is ultimately a review issue, positive results in Study NB-304 may merit (b) (4) (b) (4) It should be noted that the indication would be weight-loss in this population, not for treatment of the (b) (4) Any data generated on improvement in (b) (4) would be in the (b) (4) rather than the (b) (4)

Of note, the protocol for Study NB-304 should include the following:

- Escape criteria and/or a rescue medication algorithm for poor glycemic control.
- An algorithm for lowering or elimination of oral hypoglycemia or insulin dose based on fasting glucose levels and/or HbA1c (for patients who lose clinically significant amounts of weight).
- Hypoglycemia safety monitoring (See: Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care*. 2005 May; 28(5): 1245-9).
- A secondary efficacy analysis of oral hypoglycemic medication dosage changes, % requiring rescue medications, or % requiring discontinuation based on poor glycemic control.

Additional Sponsor Comment

Orexigen noted that the bulleted recommendations were already included in the protocol for Study NB-304.

Additional DMEP Comment

The Division will take another look at the protocol and respond.

Post-Meeting Addendum

After reviewing the entire protocol, the Division agrees that all information requested in the first three bullets is already incorporated into the study.

A post-meeting inquiry has determined that the sponsor plans to add the fourth bullet to their proposed statistical analysis plan (SAP) for NB-304.

Please note: the Division requests that the information described in bullet #4 be incorporated into the protocol for study NB-304, as well as the SAP:

- A secondary efficacy analysis of oral hypoglycemic medication dosage changes, % requiring rescue medications, or % requiring discontinuation based on poor glycemic control.

Question 12:

As requested by the Agency in the meeting with Orexigen on April 24, 2006, Orexigen plans to enroll subjects from studies NB-301 or NB-303 to participate in a study where they will undergo dual-energy X-ray absorptiometry (DEXA) scanning at baseline and after approximately 6 months of double-blind therapy. Orexigen has already conducted and analyzed results from DEXA (b) (4) scans in 39 subjects who received blinded placebo, individual product constituents, or NB 16, 32 or 48 in study NB-201 and provided 6 months follow-up data (Summary results from the phase II study are provided in Appendix 7).

A protocol outline of the planned phase III DEXA study is also provided in Appendix 6 Orexigen intends to enroll approximately 180 to 240 subjects into the phase III DEXA study, approximately half of which would also undergo (b) (4) to assess treatment effects on visceral fat. Orexigen believes that the results of the DEXA (b) (4) will provide results that may be important to the prescribing physician.

Does the Agency agree that the results of the DEXA (b) (4) may be appropriate for inclusion in the drug product labeling?

DMEP Response:

While this is ultimately a review issue, positive results in the DEXA (b) (4) may merit inclusion in the Clinical Studies section of the labeling.

As Study NB-301 and NB-303 are both 52-week studies, please comment on why the DEXA and (b) (4) will be done at 6-months and not at the end of the study.

Additional Sponsor Comment

Orexigen explained that the DEXA and (b) (4) were scheduled for 28 weeks in order to improve compliance.

Additional DMEP Comment

The Division requested that the (b) (4) be conducted at the end of the studies (one year).

Question 13:

In Study NB-303, Orexigen plans to enroll approximately 1500 obese subjects who will be randomized in a 2:1 ratio to receive NB32 or placebo, for up to 13 months. Subjects who fail to lose at least 5% of baseline body weight after at least 28 weeks of double-blind therapy and were receiving naltrexone SR 32 mg/bupropion SR 360 mg /day (NB32) may be re-randomized in a 1:1 ratio to double blind treatment with either continued NB32 or increased to naltrexone SR 48 mg/bupropion SR 360 mg /day (NB48). Subjects receiving placebo will remain on placebo. Subjects will continue to take two tablets BID. All treatment assignments will remain double blind. Orexigen believes that the re-randomized sample may allow for assessment of potential use of NB48 in patients with insufficient clinical response to NB32.

Does the Agency agree that the efficacy, safety and tolerability results of the NB48 treatment group in Study NB-303 may be appropriate for (b) (4)?

DMEP Response:

Since you do not know a priori how many patients will be switched to the 48 mg dose of Naltrexone, it is difficult for us to answer this question. We do have concerns that the Naltrexone SR 48 mg dose may not contribute sufficient efficacy to the combination to offset the possible increased safety risk and tolerability issues of this higher dose. Please refer to the responses in Question #15 for additional detail.

Please clarify the decision-making process pertaining to the possible re-randomization of patients in the active treatment arm either at week 28 or at week 32 to the Bupropion + Naltrexone 48 mg dose. While we concur with the use of LOCF imputation for these patients at the point of switching to the higher dose, for purposes of the primary efficacy evaluation, we are concerned with the interpretability of study data after patients are switched to the higher dose.

Additional Sponsor Comment

Orexigen explained that blinded non-responders would be re-randomized to the higher dose, NB48 (48 mg naltrexone SR/360 mg bupropion) or continue on NB32. The primary endpoint will be NB32 vs placebo and NB48 vs NB32 will be a secondary endpoint.

Additional DMEP Comment

We have no problem with the concept of this design, the issue is the % of patients requiring up-titration and % efficacy at the higher dose. The NB48 dose may require more studies either pre- or post-approval.

In Study NB-303, please clarify the protocol for re-randomizing subjects at week 28 and at weeks 32-44. The phrase "subjects may be re-randomized" does not adequately describe the basis for establishing the subgroup of re-randomized patients.

Question 14:

Based upon the minutes from the April 24 2006 guidance meeting between Agency representatives and Orexigen Therapeutics (see Appendix 1), Orexigen is conducting two Phase III studies that include subjects who are smokers. Orexigen believes that positive, replicated results on the co-primary objectives in these two studies may allow a (b) (4) in smokers. Additional analyses will also be performed to assess the effects of active (NB) treatment compared with placebo treatment in selected special populations such as hypertensive and dyslipidemic patients. Orexigen believes that positive, replicated results on the co-primary objectives in these special populations in at least two studies may also be (b) (4). Details on subgroup analyses are described in Appendix 4.

Does the Agency agree that if the co-primary objectives demonstrate statistically significant differences between active and placebo treatment in smokers and other special populations, those finding could be (b) (4)?

DMEP Response:

To clarify our previous comments on this issue, we asked for smokers to be included in Phase III studies because smokers were being excluded from all studies. Any data generated on improvement in smokers as a selected special population would be viewed as part of the overall efficacy of the drug product. (b) (4)

Additional Sponsor Comment

The sponsor would like to include a description of the results (related to smokers and other sub-populations) in the (b) (4)

Additional DMEP Comment

Our comments were designed to convey our recommendation that the trial database should include a broad range of patients, including smokers and other subpopulations.

Question 15:

Are there any additions or changes to the guidance the Agency provided to Orexigen in April 24, 2006 on the development of the Naltrexone-Bupropion combination for the treatment of obesity?

Does the Agency note any deficiencies in the proposed nonclinical or clinical plans?

DMEP Response:

Approval of a fixed-dose combination product requires robust evidence that the combination is more effective than the individual components and/or provides a more favorable risk-benefit profile for weight loss than the individual components of the combination. While the summary results of Study NB-201 suggest that both the naltrexone 16 mg and 32 mg components and the bupropion component have a statistically significant contribution to average weight loss in the combination products, the contribution of the naltrexone component is relatively small. In

addition, naltrexone also appeared to make a small contribution to the efficacy of the combinations in Studies OT-101 and OT-102. For these reasons, we request an additional Phase 3 study comparing the components to the combination product.

For the additional Phase 3 study, we recommend a 24-week study with a minimum of 4 arms: placebo, Naltrexone SR 32mg, Bupropion SR 360 mg, Nalt SR 32/Bup SR 360. If you wish to pursue marketing of the (b) (4) then you would need to add a (b) (4) (b) (4) monotherapy arm and a (b) (4)/Bup SR 360mg arm. We estimate that between 180 and 450 subjects would need to be randomized to each arm. This range was calculated from the following estimates: (b) (4)

As an alternative to the above recommendation, you could add the appropriate monotherapy arms to one or more of the planned phase 3 studies.

Robust evidence that the combination is more effective than the individual components will be supported by: (1) Confirmation of the statistically significant contribution of each component to the efficacy of the combination product; and (2) Consistent and supportive results from sensitivity analyses of the primary efficacy endpoints in each study separately.

- Due to the known hypertensive effects of bupropion, we recommend 24-hour ambulatory blood pressure monitoring (ABPM) in a subset of normotensive and hypertensive subjects in a phase 3 trial at baseline, Month 6 and Month 12.
- The ECGs you plan to obtain in studies 301 and 303 should be timed to coincide with C_{max} of the active drug product.

Throughout the Phase 3 studies, the following should be monitored:

- The number of subjects requiring new or increased doses of hypertensive medications.
- Any subject who develops on a single visit mean diastolic blood pressure (DBP) ≥ 95 mm Hg or an increase in DBP ≥ 10 mm Hg from baseline, or mean systolic blood pressure (SBP) ≥ 150 mm Hg or increase in SBP ≥ 15 mm Hg from baseline or pulse rate ≥ 10 bpm from baseline should be re-evaluated within 72 hours. Subjects with consistently elevated blood pressure or pulse measurements (as defined above) should be considered outliers and treated in a manner consistent with standard of care.

Given that sibutramine, a weight-loss drug also associated with small-to-modest mean increases in systolic and diastolic blood pressure and pulse rate, is currently being evaluated in a large cardiovascular outcomes study, it is possible, depending on the blood pressure data to be obtained with your product, that a similar study would be required for a fixed-dose combination of Bupropion and Naltrexone.

If you have not already done so, you should contact (b) (4) to obtain information regarding the use of the (b) (4) in your

phase 3 studies. The (b) (4) and the (b) (4) (b) (4) should be given to every patient at every visit.

Please refer to Response #8 for Clinical Pharmacology comments.

Additional Sponsor Comments

Orexigen clarified that benefit from naltrexone was not for independent weight loss but, rather, to prevent plateauing of the bupropion associated weight loss. Thus, our earlier studies were not designed to compare efficacy of naltrexone monotherapy to the combination.

We can also provide 48 week data and a summary of completed studies to show that there is a good basis for moving forward.

Additional DMEP Comments

Your previous studies had relatively small sample sizes and did not include the combination formulation to be studied in phase 3 trials. We have concluded that additional studies including relevant monotherapy arms must be conducted to verify previous results and confirm safety.

However, your comments are valuable and will be discussed within FDA.

Post Meeting Addendum

After further discussion with the team and upper management (within FDA), we've made a decision to accept the phase 2 data as sufficient to support conduct of your current phase 3 program for bup + nal. We will not be requesting that you conduct an additional phase 3 trial comparing the bup-nal combinations to the individual components nor will we ask that you add monotherapy treatment arms to the ongoing or planned phase 3 studies.

Additional Sponsor Comment

Regarding the 24-hour monitoring of blood pressure, the sponsor asked if there were any key analyses of interest or a particular device that should be used.

Additional DMEP Comments

No. You should submit a proposal for review.

Additional Sponsor Comment

The sponsor noted that the components of the combination drug product have two different C_{max} s. ECGs were planned for 2, 2-4, and 4-6 hrs post dose. Orexigen will be collecting approximately 9,000 ECGs.

Additional DMEP Comments

Although you are not conducting a thorough QT study and population PK samples will likely not be collected around Tmax in your phase 3 studies, you can still gather useful information in addressing QT from your ECG data and population PK data collected in phase 3 studies for both parent and metabolites.

Additional Sponsor Comment

The sponsor noted that phase 3 studies have already started and it would be very challenging to insert the (b) (4) at this point.

They are using the IDS which they feel is a well-validated, more user-friendly tool used in primary care settings.

Additional DMEP Comments

At a minimum, you should incorporate a retrospective assessment of suicidality. We would like to see your plan for retrospective analysis.

Question 16:

Naltrexone and bupropion, the constituents of our proposed obesity treatment, are both used for the treatment of substance dependence disorders in a similar dose range and both have been extensively tested in humans through research programs and clinical practice. Neither agent has ever been scheduled. Based on the background information provided in Appendix 8, Orexigen believes that (b) (4)

Does the Agency concur with Orexigen's assessment of the (b) (4) for naltrexone and bupropion?

Controlled Substance Staff (CSS) Response:

(b) (4)

The Abuse Potential Assessment should contain the following components:

- Chemistry (including chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)
- Pharmacokinetics and pharmacodynamics (including full data on receptor binding)
- Primary data from abuse potential studies in animals and humans
- Adverse events in clinical studies related to abuse potential

- Integrated summaries of safety and efficacy (ISS and ISE)
- Information related to overdose
- Prospective assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies

The Controlled Substance Staff is available to meet with Orexigen Therapeutics to discuss the requirements for the Abuse Potential Assessment. Such meeting requests should come through the Division of Metabolism and Endocrinology Products.

Additional Sponsor Comment

The sponsor stated that they would proactively develop an abuse potential assessment plan and submit for review.

Additional Controlled Substance Staff (CSS) Comments

All abuse liability information must be supplied as part of your NDA and we will not review it before that time. You should submit proposed abuse liability protocols for review by CSS and request a guidance meeting.

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this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
11/7/2007 02:57:54 PM

Memorandum of Meeting

Meeting Date: June 4, 2014
Application Number: NDA 200063
Product Name: Contrave (naltrexone hydrochloride/bupropion hydrochloride) extended release tablets, 8mg/90mg.
Sponsor/Applicant Name: Orexigen Therapeutics
Subject: FDA concerns related to the CVOT interim analysis and unblinding of data

FDA ATTENDEES

Immediate Office of the Director

Robert Temple, M.D. Deputy Director for Clinical Science

Office of Regulatory Policy (ORP)

Nancy Hayes, Director (Acting)

ORP; Division of Information Disclosure Policy

Nancy Sager, Director, Division of Information Disclosure Policy

Office of New Drugs (OND)

John Jenkins, M.D. Director

OND; Office of Drug Evaluation II (ODE II);

Curtis Rosebraugh, M.D., MPH Director
Mary H. Parks, M.D. Deputy Director

OND; ODE II; Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D. Director
Eric Colman, M.D. Deputy Director
Jennifer Pippins, M.D. Acting Deputy Director for Safety
James P. Smith, M.D.; M.S. Clinical Team Leader
Eileen Craig, M.D. Medical Officer
Pat Madara, M.S. Project Manager
Mehreen Hai, Ph.D. Safety Project Manager

Office of Biostatistics (OB)

Lisa LaVange, Ph.D. Director

Office of Biostatistics, Division VII

Aloka Chakravarty, Ph.D. Director
Janelle Charles, Ph.D. Statistical Reviewer

SPONSOR ATTENDEES

At White Oak:

Dawn Viveash,	Sr. VP Quality and Regulatory, Orexigen
Preston Klassen,	Sr. VP/Head of Development, Orexigen
Michael Narachi,	CEO, Orexigen
Heather Turner,	Sr. VP, General Counsel and Secretary, Orexigen
Josephine Torrente,	Legal Consultant, Orexigen
Azmi Nabulsi,	Head of R&D Strategic & Professional Affairs, Takeda
Penny Fleck,	Global Program Lead, Takeda
Lawrence Roebel,	Global RA Therapeutic Area Head, Takeda

Via Phone:

Thomas Fleming,	NB-CVOT DMC Chair
Tom Bicsak,	VP Regulatory Affairs, Orexigen
Kristin Taylor,	VP/Head of Clinical Development, Orexigen
Teri Johnson, Sr.	Director, Regulatory Affairs, Orexigen

1.0 BACKGROUND

NDA 200063, Contrave (naltrexone hydrochloride/bupropion hydrochloride) extended release tablets, 8mg/90mg, indicated for chronic weight management is currently under review in DMEP (second review cycle).

On January 31, 2011, after completion of the first review cycle, a complete response (CR) letter issued. Because mean systolic and diastolic blood pressure and heart rate were statistically significantly higher in the Contrave-treated subjects compared with placebo-treated subjects, the Division had concerns about the cardiovascular safety profile of Contrave when used long-term in a population of overweight and obese subjects. Therefore, it was requested that the company conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile.

After completion of the dispute resolution process, it was determined that Orexigen could resubmit the application and, within two months of the resubmission, provide an analysis of interim data from the CVOT, also referred to as the LIGHT trial. In order to protect study integrity, the company agreed to firewall the unblinded team, which was to consist of a small, core group of individuals required for data analysis and submission to FDA.

On April 11, 2014, the Division of Biometrics VII requested a list of individuals with access or knowledge of the unblinded data or unblinded analysis results. Orexigen submitted an informal response / listing via email on April 16, 2014. Upon review of this information, DBVII had a subsequent information request sent on May 21, 2014, asking for additional details related to those with "full access," including the date full access was granted and the exact data that were shared. Orexigen responded informally, via email on May 23, 2014. An official response to both information requests was submitted to the application on May 30, 2014.

DB VII, DMEP and CDER management expressed serious concerns about the wide dissemination of interim data and the ability to maintain the integrity of the study in this situation.

A meeting was held with Orexigen on June 4, 2014, to discuss our significant concerns and the implications that the release of data may have on the approvability of the application

2.0 Discussion:

FDA opened the meeting by stating the following concerns:

- This is the first time the Agency has encountered a situation with this extent of sharing of unblinded data or interim results from an ongoing trial. FDA envisioned an academic model that would limit sharing of interim data to a few essential individuals in order to minimize the risk compromising the integrity of the study.
- Approval of the application using interim results from the LIGHT trial was based on our expectation that the ability to get definitive data to address the CV risk of Contrave post-approval would not be compromised.
- We are meeting now to more fully understand the extent of sharing of the interim data so the impact on the integrity of the remainder of the trial can be assessed.
- The items that Orexigen shared with multiple entities include tables and patient listings, which is a serious concern for the Agency. We have questions regarding the granularity of the shared data.
- Orexigen needs to explain why these decisions were made and why the company feels it will not have a negative impact on the study integrity. We need answers in order to determine if the current trial can continue and if a new study is required in order to get data we can trust to adequately assess the cardiovascular risk of CONTRAVE.
- It is important for Dr. Tom Fleming to be aware of the extent of data sharing. Last week we spoke in the abstract with Dr. Fleming about data sharing and this week we are specifically discussing Contrave with Dr. Fleming present and we want to hear his perspective of this case.

Dr. Fleming stated that he agreed with FDA about what the understanding was regarding data sharing. Earlier access to data should not come at the price of compromising the integrity of the trial. He commented that there were five key issues to consider:

1. The role of the data monitoring committee (DMC) chair is to safeguard patients, independent of the company.
2. Consistent with #1, confidentiality is critical. FDA is on-target with this issue as this has many implications if data are released, such as, treatment cross-ins, and other aspects of the trial may be affected. Dr. Fleming stated that he believed the LIGHT Trial conduct has been exemplary. The performance standards document that was created for this trial is exceptional. The data access plan (DAP) is unique and has been shared with FDA. These documents described a pre-planned strategy to maintain the confidentiality of unblinded data from the trial. Dr. Fleming noted that it is unethical to compromise trial integrity for business reasons, even if those reasons are legitimate. He stated that based

on the DAP the interim data should only be released to a core group of individuals who are essential for the regulatory submission to protect the integrity of the trial. To retain integrity, unblinded individuals should be limited to regulatory, legal and statistical classes. The corporate leaders and CEO should remain external and their knowledge of interim results is a concern.

A strength of the design is that anyone with data access would be trained and it was key that firewalls remain in place.

3. Dr. Fleming noted that he did not have knowledge of the unblinded list until the day before the meeting. This process has not been implemented in a pristine way. The extensive unblinded list indicates that the data access plan had not been implemented as hoped. Anyone with an integral role in the trial should not be unblinded. In addition, external entities related to business decisions or financing should not be unblinded. They should know nothing about the trial other than press releases. The extent of unblinding is a concern to him.
4. Dr. Fleming stated that it was his sense that the operational procedures of the trial were still intact. He noted that a great deal of care had been taken to keep those individuals involved in the regulatory submission separate from those who were blinded. The firewall was working, in spite of unblinding to management. No publicly detectable breaches have been seen. There is no evidence at this point that there is any public dissemination of the interim results.
5. Dr. Fleming stated that he still believed the trial could be completed with integrity. He noted that many in academia want to move forward in developing clear guidelines to data disclosure to maintain confidentiality of trial data. It is essential that they join forces with the FDA to make clear to sponsors the nature of the unblinded team in terms of the number of individuals that are unblinded, their specific position and that they have no involvement in business decisions.

Dr. Fleming noted it was important to set standards and the degree of unblinding was disappointing. It is not acceptable but it was a challenging situation for a small company. He was not saying everything was fine but from an operational aspect, the firewall was intact and there is a proper separation of the unblinded team and blinded team involved in the trial conduct.

FDA commented on their concern that the unblinding could lead to further unblinding to the public. The Agency is now less confident the trial can be completed and provide definitive data on the CV risk for Contrave. (b) (4)

Dr. Fleming stated that it would be a concern under any circumstances, especially to facilitate business interests. Business interests do not justify the release of data and it is unethical to compromise the trial data integrity. (b) (4)

FDA pointed out that there are multiple layers to worry about. There is a high level of uncertainty around any point estimate derived from interim data, and the estimate is likely to change with the accumulation of additional data. Also, access to tables and listings means that people could know individual treatment assignment. It is very hard to prove that no harm was done to the integrity of the trial.

Dr. Fleming agreed that there was a high degree of uncertainty and the early data were likely to be misleading. He stated that in a smaller company the logistical challenges are far greater. This is a relatively straight forward matter for a large company. Orexigen gave a great deal of attention to data flow and interaction. He is confident that the firewall is still intact. The business level of unblinding and the total number of individuals that were unblinded is concerning.

(b) (4)

Orexigen noted that they had a strong process in place to maintain the blinding. All data were kept on a secure server, accessible only to the Orexigen and Takeda teams. They pointed out that everyone involved had signed a confidentiality agreement. Vendors had been audited and a survey of the public indicated that equipoise had been maintained.

FDA commented that the slide sets Orexigen had shared contained a lot of information that business partners did not need to know.

FDA stated that business interests only need to know that the trial passed the threshold for the interim analysis. FDA asked the company why they did not just say that the upper bound was below two. Orexigen commented that would not suffice. They needed to disclose more data in order to obtain corporate financing.

FDA stated there were many issues to consider:

- The unblinding violated the company's DAP and the company has released data to more people than is necessary to support regulatory submission. Other companies have protected senior management from knowing the unblinded interim data but in Orexigen that has not happened—senior management is aware of the data. Orexigen did not seek advice from FDA or the DMC chair prior to data sharing.
- Business decisions were made based on unblinded interim results from roughly 20% of the information the trial was designed to obtain. These results had a high degree of uncertainty and were likely to change with the accumulation of additional data.
- Processes outlined in the DAP had been integral to the regulatory submission of the application. Allowing approval based on interim data was based on believing we could get a definitive answer post-approval.
- The Agency's goal was to obtain a definitive answer by completion of a valid trial. Now we are uncertain how to do this.
- Given the extent of Orexigen's unblinding of the data, FDA does not know if the interim data can be protected and confidentiality maintained until the study is completed. This may also have compromised FDA's ability to provide a rationale for why the FDA cannot disclose the data to the public. FDA has to do the analysis of whether FDA can still protect the data given the extent of the unblinding.

Dr. Fleming made the following comments prior to leaving the meeting:

- He was reluctant to provide advice. His goal was to see the trial successfully completed with integrity such that answers could be obtained.

- If the trial moves forward, we will be able to tell if the interim data have been compromised.
- We need to look into the timely enrollment of a possible second cohort. Differential treatment cross-ins may affect the trial once the drug is approved.
- He would do everything possible to safeguard the integrity of the study and would provide information related to maintaining blinded data if the study continues.

Orexigen stated that SEC disclosure requirements of corporate management require the disclosure of documents with material information. Orexigen stated that they took business and legal risk to not disclose data. They explained that in a small company, material risk is involved because they only have a few products. In a larger company, one product may not be “material” if they have a large number of products in their portfolio and thus they may not need to disclose information.

[REDACTED] (b) (4)
[REDACTED] (u) (4)

Orexigen stated that if the trial was stopped, they would be forced to disclose the interim results because lawsuits against the company would follow.

FDA stated that another option is to complete the trial before we consider approval. Orexigen stated that if Contrave was not approved, they would need to disclose some of the data as it would constitute material information and they have legal obligations to disclose and because they would need to prove it was not an efficacy or safety issue.

FDA ended the meeting by making the following comments:

- Many internal discussions would be required after this meeting and the June 11, 2014 PDUFA goal date would not be met.
- The Agency would discuss the ability to protect the data moving forward and continue the study such that results would not be compromised.
- [REDACTED] (b) (4)
[REDACTED] Differential cross-ins and the high treatment discontinuation rate are other potential issues that need to be considered.
- Extension of the review clock (major amendment) was a possibility. However, in principle, submission of a major amendment that extends the review clock occurs when an application is headed toward approval. Another possibility was to issue a complete response (CR) letter.

Post Meeting Comments

An internal meeting was held on June 5, 2014, at which time a variety of options were discussed.

On June 9, 2014, Dr. Colman held a teleconference with the company to request additional data related to the number of individuals who had access to unblinded interim results. See internal meeting minutes entered into DARRTS on June 10, 2014 (advice – verbal).

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

/s/

JAMES P SMITH
09/30/2014

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: March 11, 2013, 2:00 pm
Meeting Location: Teleconference

Application Number: NDA 200063
Product Name: Contrave (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight
Sponsor/Applicant Name: Orexigen Therapeutics, Inc.
Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

FDA ATTENDEES

Office of Drug Evaluation II/Division of Metabolism and Endocrinology Products (DMEP)

Eric Colman, M.D., Deputy Division Director
James Smith, M.D., M.S., Medical Officer
Eileen Craig, M.D., Medical Officer
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Julie Marchick, M.P.H., Chief Project Management Staff
Amy Egan, M.D., M.P.H Deputy Division Director for Safety Deputy Director
Elizabeth Chen, Pharm.D. Regulatory Project Manager

Division of Biometrics VII (DB VII), Office of Biostatistics

Mat Soukup, Ph.D., Biometrics Team Leader

Division of Biometrics II (DB II), Office of Biostatistics

Jon (Todd) Sahlroot, Ph.D., Deputy Division Director and Statistics Team Leader
Janice Derr, Ph.D., Biometric reviewer

Office of Surveillance and Epidemiology

Ermias Zerislassie, Pharm.D., M.P.H., Safety Regulatory Project Manager

Controlled Substance Staff

Chad Reissig, Ph.D., Pharmacologist

Office of Scientific Evaluation (OSI)

Sharon Gershon

SPONSOR ATTENDEES

Thomas Bicsak, Ph.D., Sr. Director, Regulatory Affairs

Orlando Bueno, M.D., Medical Director

Colleen Burns, Ph.D., Director, Biostatistics

Teri Johnson, RAC, Director, Regulatory Affairs & Development Strategic Planning

Preston Klassen, M.D., Sr. Vice President, Head Global Development

Lawrence Roebel, Ph.D., Global RA Therapeutic Area Head

Kristin Taylor, Ph.D., Sr. Director, Clinical Development

Dawn Viveash, M.D., Sr. Vice President, Regulatory Affairs

1.0 BACKGROUND

NDA 200063 was submitted by Orexigen as a 505(b)(2) combination for Contrave [naltrexone hydrochloride and bupropion extended-release fixed-dose combination] tablets (8 mg/90 mg) for the treatment of obesity and weight management, including weight loss and maintenance of weight loss. Orexigen claims both products interact in the central nervous system to decrease food intake and increase energy expenditure, resulting in synergistic and sustainable weight loss.

FDA issued a complete response (CR) letter on January 31, 2011, stating that before this application could be approved, the applicant must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. An end of review (EOR) meeting was held on May 26, 2011, and the meeting minutes were issued on June 27, 2011.

Orexigen submitted a formal dispute resolution request to the Office of Drug Evaluation II (ODE II) on June 8, 2011, concerning the complete response action taken on January 31, 2011, specifically the pre-approval requirement for a cardiovascular outcomes trial (CVOT). Dr. Curtis Rosebraugh (Director, ODE II) denied the appeal on July 7, 2011. Orexigen submitted a request for formal dispute resolution to the Office of New Drugs (OND) on July 14, 2011. Dr. John Jenkins (Director, OND) denied the appeal on September 15, 2011.

Subsequently, Orexigen submitted a Type A meeting request on October 4, 2011, to the Division of Metabolism and Endocrinology Products (DMEP), to discuss the design elements of the proposed CVOT. The meeting was granted and scheduled for November 16, 2011. The meeting minutes were issued on December 12, 2011.

Orexigen submitted a request for formal dispute resolution to the Center for Drug Evaluation and Research on August 7, 2012. Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs, was the deciding authority. In Orexigen's August 7, 2012, dispute resolution submission, the company requested a meeting with the deciding official before he rendered his decision on this matter. The meeting was granted and took place on September 6, 2012. Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs denied the appeal on October 15, 2012, with caveats about working with DMEP to expedite the resubmission.

Orexigen submitted a Type C meeting request on October 26, 2012, to DMEP, to discuss the logistics of resubmitting the NDA. The teleconference was held on January 4, 2013 and meeting minutes were issued on January 25, 2013.

Orexigen requested another Type C meeting on December 19, 2012, to DMEP, to discuss the proposed content of the NDA resubmission. The teleconference was held on March 11, 2013.

Repeated below in plain text are Orexigen's questions followed by FDA's preliminary responses written in bold text. The meeting discussion is in *italics*.

2. Sponsor Questions and FDA Preliminary Responses

Content and Format of the Resubmission

Sponsor Question 1: Does the Division agree with the proposed content and format of the NDA resubmission, including the proposed content of the NB-CVOT interim data CSR and Safety Update Report?

FDA Response: Yes, we agree. However, if during our review there are other analyses that we will need, please confirm that there will be a firewalled, unblinded study team that will be available to do these analyses upon request.

Please include in your submission the following:

- Conduct analyses on the hazard ratio of Contrave vs. placebo for each of the three components of the primary MACE: cardiovascular death, nonfatal myocardial infarction and nonfatal stroke
- Subgroup analyses of the hazard ratio of MACE by baseline demographic characteristics (gender, race and age)
- Subgroup analyses of the hazard ratio of MACE by baseline cardiovascular risk factors (such as BMI, hypertension, hyperlipidemia, renal function impairment, smoking status and, in subjects with diabetes, duration of diabetes).
- Include tables with data on the mean, standard deviation, median, interquartile range, and minimum/maximum values for systolic blood pressure, diastolic blood pressure and heart rate for the two groups at each study visit.

Meeting Discussion: Applicant confirmed that they will have a firewalled team available to conduct analyses upon request. Applicant will assess the number of subjects of subgroups for valid analysis. FDA had no further comments.

Sponsor Question 2: Are there any other topics or procedures not mentioned in the CRL that need to be addressed either prior to or in the resubmission to allow the Division to complete their *review of the NDA*?

FDA Response: Please see comments at the end of the letter.

Meeting Discussion: Applicant inquired about the site-level dataset, seeking to clarify that the "treatment efficacy result" variable referred to MACE and not other efficacy assessments. FDA confirmed that this was the case, responding that the FDA preliminary comments provided were from a common template and not specific to this application.

Contrave Risk Evaluation and Mitigation Strategy (REMS)

Sponsor Question 3: Does the Division agree that the requirement for a REMS to support Contrave approval is dependent on the results of the NB-CVOT interim analysis?

FDA Response: Based on the information available at this time, we do not believe that a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of CONTRAVE (naltrexone/bupropion) outweigh the risks. If, however, during the course of our review we make a determination that a REMS will be necessary, we will notify you of our determination and the safety issue(s) that forms the basis for it.

Meeting Discussion: No further discussion.

Contrave Labeling

(b) (4)

(b) (4)

(b) (4)

Sponsor Question 5: In light of ongoing discussions within the Agency, has the Agency's opinion regarding disclosure of interim clinical trial data changed relative to the 10 July 2012 communication to Orexigen on this subject?

Sponsor Question 6: Does the Division agree that if Study NB-CVOT interim data will be disclosed in the summary review documents, Contrave labeling will include an appropriate level of interim data as well?

FDA Response to Question 5 and 6: FDA remains actively engaged in internal discussions regarding the disclosure of interim clinical trial data, but at this time, no policy decisions have been made that would apply to Study NB-CVOT. Therefore, it is premature to discuss whether Study NB-CVOT interim data would be disclosed in the summary review documents or whether Contrave labeling could include any interim data from Study NB-CVOT. As soon as a final policy decision has been made regarding the disclosure of interim data, we will provide you with an update regarding this topic.

Meeting Discussion: No further discussion.

Proposed Contrave Treatment Algorithm

Sponsor Question 7: Does the Division agree that the proposed criterion of at least 5% weight loss at Week 16 to continue treatment, and the general guidance to discontinue treatment in the face of sustained elevations in blood pressure or heart rate, will support the appropriate use of Contrave?

FDA Response: Your general guidance to discontinue treatment in the face of sustained elevations in blood pressure or heart rate appears reasonable. We may consider adding in a suggested guideline to discontinue treatment if a patient experiences sustained increases in blood pressure (systolic or diastolic) of ≥ 10 mm Hg as that was what was studied in the CVOT.

We believe that the proposed criterion to discontinue Contrave at week 16 if a patient has not lost at least 5% of initial body weight may be reasonable. However, to enable us to evaluate this criterion further, we request the following additional information:

1. Tabulate the sensitivity and specificity for identifying 5% non-responders at the week 56 endpoint for each of the four Phase 3 studies separately, using the same range of early visits and early weight loss thresholds that are shown in Table 2, Appendix 5 of the briefing document. We request that sensitivity and specificity be re-defined so that sensitivity refers to correctly identifying a 5% non-responder at week 56, based on being classified as an “early weight loss [*threshold level*]” non-responder. Continue to use the FAS/LOCF analysis sets as you did in the briefing document. The reasons for these modifications are as follows:
 - a. We would like to reference the non-responders in the sensitivity/specificity calculations in order to be consistent with similar tabulations that were done with Belviq™ and Qsymia™. These tabulations also used the FAS/LOCF analysis sets.
 - b. We would like to see the results tabulated separately for the four

Phase 3 studies due to the differences in study design and patient population among the studies. A separate tabulation by study will permit an informal assessment of the consistency of results among the studies.

2. For Study NB-303, provide a separate cross-tabulation that classifies subjects according to whether or not they were identified as 5% non-responders during weeks 28-44, whether or not they were re-randomized to receive the 48 mg dose of naltrexone in the combination product, and whether or not they were 5% responders at week 52. We would like to understand the extent to which this step in the protocol contributes to the overall estimate of sensitivity and specificity at week 52.
3. Tabulate the results from the combined results of the studies that were conducted on non-diabetic subjects, both with and without Study NB-303. Describe the method that you used to combine results across studies. Our reason for this request is to be consistent with similar tabulations that were done with Belviq and Qsymia on non-diabetic subjects.
4. Include a description of how “accuracy” was calculated for the study results. We note that our focus is on the sensitivity and specificity of the classification of early weight non-responders in relation to the classification of 5% non-responders at week 56. This focus has developed from our work with Belviq and Qsymia. For example, the label for Belviq includes the following: “Discontinue if 5% weight loss is not achieved by week 12.” This recommendation was based on the relationship between the amount of weight loss at week 12 and the amount of weight loss at the 52-week endpoint in the lorcaserin studies.

Meeting Discussion: No further discussion.

Assessment of Contrave Abuse Potential

Sponsor Question 8: Can the Division confirm that sufficient information has been provided and that review by CSS has occurred to support that Contrave will not need post-approval scheduling assessments?

FDA Response:

- Overall, the abuse potential of Contrave does not warrant scheduling or control under the CSA at this time. However, new data included in the NDA resubmission (e.g. data from clinical trials examining the cardiovascular effects of Contrave) may affect this conclusion.
- If Contrave is approved and post-marketing epidemiological data show evidence of misuse and abuse, the abuse potential of Contrave will be re-evaluated and may be scheduled under the CSA at a later date.

- **CSS has no further recommendations at this time.**

Meeting Discussion: No further discussion.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see Warnings and Precautions (5.2)]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

FDA Response to Question 2: Although the standard language below refers to original NDA submissions and completed phase 3 clinical trials, we are requesting that you provide the same information with your complete response, using the interim results of NB-CVOT.

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

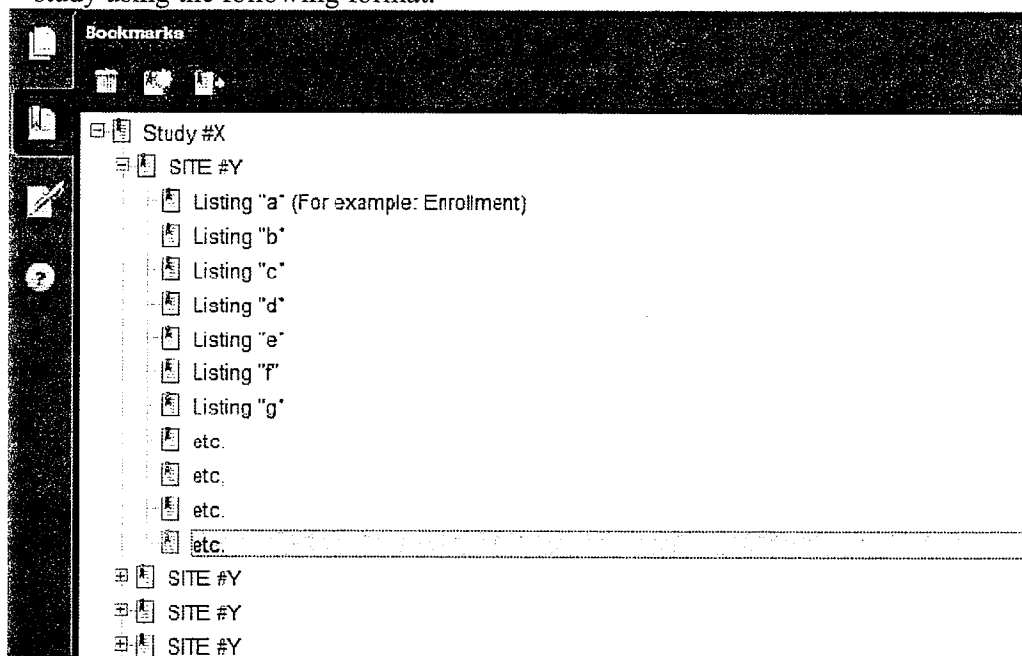
1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number

- b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
 4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
 5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates

- g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis

- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Reference ID: 3290727

Reference ID: 3632020

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

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 Meeting Minutes
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MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Reference ID: 3290727

Reference ID: 3632020

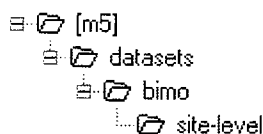
Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

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Meeting Minutes

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

3.0 No issues requiring further discussion.

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

/s/

ERIC C COLMAN
04/09/2013

1-31-2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200063

MEETING MINUTES

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines Court, Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 4, 2013. The purpose of the meeting was to discuss the logistics of resubmitting your NDA.

A copy of the official minutes of the teleconference 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) 796-796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, 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: January 4, 2013 from 1:00 pm to 2:30 pm
Meeting Location: Teleconference

Application Number: NDA 200063
Product Name: naltrexone hydrochloride and bupropion hydrochloride extended-release tablets
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss
Sponsor/Applicant Name: Orexigen Therapeutics, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

FDA ATTENDEES:

Office of Drug Evaluation II/Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D., Division Director
Eric Colman, M.D., Deputy Division Director
Eileen Craig, M.D., Medical Officer
James Smith, M.D., M.S., Medical Officer
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Pam Lucarelli, Acting, Chief Project Management Staff
Amy Egan, M.D., M.P.H., Deputy Director for Safety

Division of Biometrics VII (DB VII), Office of Biostatistics

Mat Soukup, Ph.D., Biometrics Team Leader

SPONSOR ATTENDEES

Orexigen Therapeutics, Inc.

Dawn Viveash, M.D., Sr. Vice President, Global Regulatory Affairs
Thomas Bicsak, Ph.D., Sr. Director, Regulatory Affairs
Colleen Burns, Ph.D., Director, Biostatistics
Teri Johnson, RAC, Director, Regulatory Affairs & Development Strategic Planning

NDA 200063
Meeting Minutes
Type C Guidance

Preston Klassen, M.D., Head of Global Contrace Program & Sr. VP of Product
Development
Kristin Taylor, Ph.D., Sr. Director, Clinical Development

Takeda Global Research & Development Center, Inc.
Lawrence Roebel, Ph.D.

Outside consultants

Josephine Torrente, MS, JD, Regulatory Consultant, Hyman, Phelps & McNamara, P.C.

1.0 BACKGROUND

NDA 200063 was submitted by Orexigen as a 505(b)(2) combination for fixed dose product: Contrave [naltrexone hydrochloride and bupropion extended-release] tablets (8 mg/90 mg) for the treatment of obesity and weight management, including weight loss and maintenance of weight loss. Orexigen claims both products interact in the central nervous system to decrease food intake and increase energy expenditure, resulting in synergistic and sustainable weight loss.

FDA issued a complete response (CR) letter on January 31, 2011, stating that before Orexigen's application could be approved, the applicant must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. An end of review (EOR) meeting was held on May 26, 2011, and the meeting minutes were issued on June 27, 2011.

Orexigen submitted a formal dispute resolution request to the Office of Drug Evaluation II (ODE II) on June 8, 2011, concerning the complete response action taken on January 31, 2011, specifically the preapproval requirement for a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. Dr. Curtis Rosebraugh, Director, ODE II denied the appeal on July 7, 2011. Orexigen submitted a request for formal dispute resolution to the Office of New Drugs (OND) on July 14, 2011. Dr. John Jenkins, Director, OND denied the appeal on September 15, 2011.

Subsequently, Orexigen submitted a Type A meeting request on October 4, 2011, to Division of Metabolism and Endocrinology Products (DMEP), to discuss the design elements of the proposed CVOT. The meeting was granted and scheduled for November 16, 2011. The meeting minutes were issued on December 12, 2011.

Orexigen submitted request for formal dispute resolution to the Center for Drug Evaluation and Research on August 7, 2012. Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs, was the deciding authority. In Orexigen's August 7, 2012, dispute resolution submission, the company requested a meeting with the deciding official before he rendered his decision on this matter. The meeting was granted and took place on September 6, 2012. Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs denied the appeal on October 15, 2012 with caveats about working with DMEP to expedite the resubmission.

Orexigen submitted this current Type C meeting request on October 26, 2012, to DMEP, to discuss the logistics of resubmitting the NDA. The teleconference was held on January 4, 2013.

Repeated below in regular text are Orexigen's questions followed by FDA's preliminary responses written in **bold** text. The meeting discussion is in *italics*.

2.0 Sponsor Questions and FDA Response

Sponsor Question 1: Does the Division support resubmission of the Contrave NDA, provided that results of the interim analysis can be provided at (b) (4) during the review period without automatically triggering a major amendment?

Sponsor Question 2: Does the Division agree that a summary report based on data reviewed by (b) (4) that the data support resubmission can be the means of providing interim data to the Division during review?

Sponsor Question 3: Does the Division agree that the complete clinical study report describing the interim analysis can be provided after completion of the resubmission review?

FDA Response: We do not agree with your proposed timeline for resubmission. Our expected standard is that a complete application will be presented at the time of the NDA resubmission. However, given the aforementioned regulatory history, we are willing to accept less than a complete application at the time of resubmission, as detailed below.

1. The submission of the DMC NB-CVOT interim analysis summary report based on ≥ 87 adjudicated MACE that will include information on the point estimate and the confidence intervals will re-start the clock. The DMC datasets used to generate this report should also be included along with a Define file documenting data set structure(s) and variables.

2. The interim data CSR, including analysis data sets, must be submitted to FDA within 60 days of submissions of the DMC NB-CVOT interim analysis summary report. Failure to do so may result in a complete response action or an extension of the review clock. To facilitate the review of the analysis data set provided within 60 days of submission of the DMC NB-CVOT interim analysis summary report, we request that you provide an example data set at the time of submission for us to understand the structure of the data set and the variables that will be included. Note that at time of submission of the interim data CSR, at minimum, we request data on the following:

- Disposition
- Demographics and baseline characteristics, including baseline cardiovascular risk factors
- Concomitant medications
- MACE related information (date of event, adjudication, etc.)

Meeting Discussion:

Orexigen commented that the trial is nearing complete enrollment with approximately 9000 subjects randomized from 270 clinical trial sites. The percentage of subjects with diabetes and CVD are consistent with the targets proposed for the trial. The trial is sufficiently powered based on assumptions of key parameters that were determined prior to study initiation. All subjects will

be followed until the end of the trial, regardless of adherence to study drug. Approximately 90% of subjects are on lipid lowering therapies, which is higher than expected. They are targeting a 1-1.5% annual rate of MACE. The DMC is scheduled to compare the actual and expected event rates at the end of February.

Orexigen discussed their proposal for re-submission and wanted to know if FDA would consider re-starting the Prescription Drug User Fee Act (PDUFA) clock with a submission that did not include interim results from the cardiovascular outcomes trial (CVOT).

*(b) (4)
(b) (4) FDA
clarified that we are willing to be flexible and restart the PDUFA clock with the DMC report and its supporting datasets, but the full analysis datasets and clinical study report (CSR) must be submitted within 60 days. These points are described in more detail in FDA responses #1 and #2.*

Sponsor did not agree with the FDA proposal but stated that they will have an internal discussion and get back to us.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Sponsor stated that they will have an internal discussion and get back to FDA about our proposal.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor stated that they would have an internal discussion and get back to FDA about our proposal	Sponsor	No date was discussed

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

/s/

MEGHNA M JAIRATH
01/31/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200063

MEETING MINUTES

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines, Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended Release tablets, 8 mg/90 mg.

We also refer to the meeting between representatives of your firm and the FDA on November 16, 2011. The purpose of the meeting was to discuss the design elements of the proposed cardiovascular outcomes trial (CVOT).

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) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, 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: A
Meeting Category: Guidance

Meeting Date and Time: November 16, 2011, from 10:00 am to 11:00 am
Meeting Location: FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, Maryland, 20993

Application Number: NDA 200063
Product Name: CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended Release tablets, 8 mg/90 mg
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss
Sponsor/Applicant Name: Orexigen Therapeutics, Inc.

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

CDER ATTENDEES:

Clinical Science

Robert Temple, M.D. Deputy Director

Office of New Drugs

John Jenkins, M.D. Director

Office of Drug Evaluation II (ODE II)

Curtis Rosebraugh, MD, ODE Director

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D., Division Director

Meghna M. Jairath, Pharm.D., Regulatory Project Manager

Julie Marchick, M.P.H., Acting Chief, Project Management Staff

Eric Colman, M.D., Deputy Director

Eileen Craig, M.D., Primary Reviewer

Amy Egan, M.D., Safety Deputy Director

John Bishai, Ph.D., Safety Regulatory Project Manager

Abolade Adeolu, R.Ph., M.S., MBA, Regulatory Project Manager

NDA 200063
Meeting Minutes
A

Division of Biometrics VII (DB VII), Office of Biostatistics

Xiao Ding, Ph.D., Biometrics Reviewer
Mat Soukup, Ph.D., Biometrics Team Leader
Aloka Chakravarty, Ph.D., Division Director

SPONSOR ATTENDEES

Orexigen Therapeutics, Inc.

Dawn Viveash, M.D., Sr. Vice President, Global Regulatory Affairs
Thomas Bicsak, Ph.D., Sr. Director, Regulatory Affairs
Colleen Burns, Ph.D., Director, Biostatistics
Teri Johnson, RAC, Director, Regulatory Affairs & Development Strategic Planning
Preston Klassen, M.D., Head of Global Contraceptive Program & Sr. VP of Product Development
Kristin Taylor, Ph.D., Sr. Director, Clinical Development

Takeda Global Research & Development Center, Inc.

Cong Han, Ph.D., Senior Manager, Statistics
Prabhakar Viswanathan, M.D., Ph.D., Medical Director, Clinical Science (Diabetes & Metabolism)

Outside consultants

[REDACTED] (b) (4)

Josephine Torrente, M.S., JD, Regulatory Consultant, Hyman, Phelps & McNamara, P.C.
[REDACTED] (b) (4)

1.0 BACKGROUND

NDA 200063 was submitted by Orexigen as a 505(b)(2) combination for fixed dose product: Contrave [naltrexone HCl and bupropion extended release] tablets (8 mg/90 mg) for the treatment of obesity and weight management, including weight loss and maintenance of weight loss. Orexigen claims both products interact in the central nervous system to decrease food intake and increase energy expenditure, resulting in synergistic and sustainable weight loss.

FDA issued a complete response (CR) on January 31, 2011, stating that before Orexigen's application could be approved, they must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. An end of review (EOR) meeting was held on May 26, 2011, and the meeting minutes were issued on June 27, 2011.

Orexigen submitted a formal dispute resolution request to the Office of Drug Evaluation II (ODE II) on June 8, 2011, concerning the CR action, specifically the preapproval requirement for a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. Dr. Curtis Rosebraugh, Director, ODE II denied the appeal on July 7, 2011. Orexigen submitted a formal dispute resolution request to the Office of New Drugs on July 14, 2011. Dr. John Jenkins, Director of the Office of New Drugs denied the appeal on September 15, 2011, which outlined detailed elements of a cardiovascular outcomes trial (CVOT) design that would meet the requirements set forth in the CR letter.

Subsequently, Orexigen submitted a Type A meeting request on October 4, 2011, to DMEP, to discuss the design elements of the proposed CVOT.

Repeated below in regular text are Orexigen's question followed by FDA's preliminary responses written in **bold** text. The meeting discussion is highlighted in *italics*.

2. DISCUSSION

2.2 GENERAL (QUESTIONS FROM THE MEETING REQUEST)

Sponsor Question 1: Does the Division agree in general with the proposed CV outcomes trial design?

FDA Preliminary Comment:

Primary endpoint: Please refer to our comments for Question #3 regarding the primary composite endpoint. We believe the appropriate primary endpoint for this non-inferiority trial is major adverse cardiac events (MACE) defined as cardiovascular (CV) death, nonfatal myocardial infarction (NFMI), and nonfatal stroke. (b) (4)

Secondary endpoint: You have proposed to include the proportion of subjects with a (b) (4) analyses. This analysis may only be considered as exploratory as it will be based on (b) (4)

Sponsor Question 2: Does the Division agree with the following specific aspects of the proposed CV outcomes trial as detailed in the protocol:

Meeting Discussion: None

a) Study design and schema?

FDA Preliminary Comment: No. A more thorough description of the following items needs to be provided in a revised protocol.

1. Information on the randomization procedures is not sufficiently addressed in the current protocol. The following information should be provided in your revised protocol.

- **Process of randomization:** Describe how randomization will be performed (e.g. whether a centralized system such as an interactive voice response system will be used). In addition state whether a simple stratification procedure will be used or if block randomization will be provided.
- **Stratification:** In section 9.9, the sponsor proposed that baseline CV risk group will be used as a stratification factor for the randomization. The sponsor should clarify whether any other stratification factors will be incorporated into the randomization scheme (e.g. site or any of the covariates for which the primary analysis will be adjusted – sex, age).

Meeting Discussion: None

2. Since the proposed trial design includes both a single-blinded lead-in phase and a double-blinded treatment phase along with a proposal to include multiple interim analyses and multiple hypotheses testing, it is very important to specify how the blindness will be maintained throughout the whole trial. This is critical to maintain the quality and integrity of the proposed CV outcome trial. The following items should be addressed in regards to study blinding.

- **Provide a finalized Data Monitoring Committee (DMC) charter.**
- **Provide details for when to break the blindness of treatment assignment and when the database will be locked for the first stage analysis to rule out the non-inferiority margin of 2.0.**
- **Provide a description of measures planned to be taken in order to maintain the blindness after conducting the first stage analysis to rule out NI margin of 2.0 and continue the trial for the final stage analysis to rule out NI margin of 1.4.**

Meeting Discussion: None

b) Approach to data collection, including handling of MACE endpoints, blood pressure data, and proposed efficacy and safety measures?

FDA Preliminary Comment: In general, yes. We note that laboratory assessments will only be done at the beginning of the trial and data on concomitant medications will only be collected at the beginning and end of the trial. This will limit the ability to assess for changes in medications for hypertension or diabetes and we will not be able to assess for changes in HbA1c or lipids during the trial.

We also note that routine safety data collection will be limited to adverse events leading to discontinuation of study medication and SAEs. Information on in-utero exposures and pregnancy outcomes will be collected. Safety data will be reviewed on an ongoing basis by an independent DMC.

When submitting the protocol for the cardiovascular safety outcomes trial, please provide:

- **Definitions for all primary , secondary and other endpoints and events of special interest**
- **Case Report Form for capturing cardiovascular events**
- **Clinical Endpoints Committee (CEC) Charter, including algorithms to be used for cardiovascular endpoint events**

- **Statistical Analysis Plan (SAP) or detailed statistical section of the study protocol**

Meeting Discussion: None

c) Sample size?

FDA Preliminary Comment: Based on the assumptions provided in the protocol, the proposed sample size is reasonable.

What percentage of the 300 centers for the trial will be in the United States?

Meeting Discussion: Orexigen stated that they are planning for all sites to be in the United States.

What attempt will be made for inclusion of more non-white individuals into the CVOT?

Meeting Discussion: Orexigen stated that they will include their plans for enrollment of a more racially diverse population when they submit the protocol.

d) Statistical analysis and testing strategy?

FDA Preliminary Comment:

1. It is acceptable to include covariates other than the treatment (sex, age, baseline CV risk group) in the primary analysis model. However, please provide clarifications on the following points.

- **For age, please clarify whether it will be included in the Cox regression model as a continuous variable or a categorical variable. If age categories will be used, definition of the categories should be pre-specified in the protocol.**
- **For baseline CV risk group, please clarify what is the meaning of “each potentially with additional risk factors” (draft protocol page 36 Section 9.4.7). The total number of risk groups (i.e. levels of baseline CV risk), as well as a detailed definition of each group, should be pre-specified in the protocol.**
- **Other covariates to be included, in addition to age, are gender and race.**

- **Cox regression model with only one covariate of treatment should also be conducted as a sensitivity analysis. Unlike the case of regular linear regression model, to include more covariates in a Cox regression model will not always result in treatment effect estimate with more precision. Furthermore, for the first stage analysis to rule out NI margin of 2.0, the Cox regression model will be based on no more than 88 events. With the relatively small number of events, the impact of including several additional covariates (sex, age, baseline CV risk groups) in the Cox regression model need to be assessed.**

2. Given the results from the primary Cox regression model, it is not clear how the sponsor plans to test each of the 3 null hypotheses (H01, H02, H03). Whether two-sided confidence interval or one-sided interval will be used for the hypotheses testing should be specified in your revised protocol.

3. The sponsor proposed to utilize a (b) (4) to ensure strong control of the family-wise type 1 error rate. It should be noted that the (b) (4) (b) (4) is normally applied to address multiplicity issues arising in the analysis of clinical trials with multiple endpoints and/or multiple dose levels. It is not commonly used when interim analyses are involved. In this case, the proposed testing strategy should be viewed as a sequential testing strategy rather than a (b) (4) (b) (4). In the trial proposed, we consider testing to be conducted at two stages: Stage 1 corresponds to ruling out a HR of 2.0 (H01) and Stage 2 corresponds to ruling out a HR of 1.4 (H02) (b) (4) (b) (4).

4. It is statistically acceptable to use the full alpha to sequentially test the 3 null hypotheses in the order of H01→H02→H03. The proposed testing strategy should be able to correctly control the overall type 1 error rate if any of the following three events occur.

- A. When the true hazard ratio for NB32 relative to placebo is ≥ 2.0 , falsely approve NB32 at the time of first stage analysis**
- B. When the true hazard ratio for NB32 relative to placebo is ≥ 1.4 , falsely conclude NB32 is safe enough to stay on the market at the time of final stage analysis.**

In other words, the probability of event A, B, or C occurs is less than 2.5%. Furthermore, the probability of any two or even all three of the three events occur is also controlled to be less than 2.5%.

It should be noted that at Stage 1 (i.e. ruling out a HR of 2.0) for which the product will be evaluated for approval, there is no guarantee that at Stage 2 the trial will be able to rule out HR of 1.4 based upon a sequential testing procedure. Determination of the trial to meet study objectives at Stage 2 based on data from Stage 1 should be evaluated by calculating conditional power or through simulation. Determination of approvability at Stage 1 will ultimately be a review issue.

Meeting Discussion: None

2.3 QUESTIONS INCLUDED IN THE BRIEFING DOCUMENT

PRIMARY ENDPOINT

Sponsor Question 3: Does the Division agree with the use of a ^(b)₍₄₎ component composite endpoint ^(b)₍₄₎ as the primary study endpoint?

FDA Preliminary Comment: As we have stated in previous correspondence including the End-of-Review meeting and the Formal Dispute Resolution Requests, we believe that the appropriate MACE endpoint for this non-inferiority trial consists of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

“Softer” endpoints, such as revascularizations, hospitalization for unstable angina, and hospitalization for heart failure, are more subjective, can be challenging to define, and may differ depending on the local community standard of care. The variability of these more subjective endpoints can bias results towards showing no difference between treatment groups. We are aware that ^(b)₍₄₎ ^(b)₍₄₎ has been allowed in the primary composite endpoint for some non-inferiority CVOT of antidiabetic agents. However, we believe strict MACE should be the primary endpoint for the proposed Contrave non-inferiority CVOT.

Meeting Discussion:

We stated the following:

- *There are several reasons why we are requesting MACE for the primary endpoint.*
- *One of the reasons why you were asked to conduct this CVOT is because of sibutramine and the findings from SCOUT, which used MACE as a primary endpoint. We want this trial to capture the same or similar primary endpoints*

evaluated in SCOUT to reassure us that Contrave is not behaving like sibutramine.

In the Contrave trial, unlike in most of the diabetes trials, we are evaluating a drug where we have identified a CV safety signal. We are more concerned about any potential bias or noise in the trial design. The variability of more subjective endpoints, such as revascularizations, hospitalization for unstable angina, and hospitalization for heart failure, can bias results towards showing no difference between treatments. As such, and considering the typically higher drop out rate in obesity trials and the ITT evaluation as opposed to the per-protocol population as the primary analysis population, we are concerned about adding a less objective endpoint.

- In addition, if we had a concern with a diabetic drug, we most likely would require MACE as the primary endpoint. Case in point is rosiglitazone and the TIDE trial where we required MACE as the primary composite (the first occurrence of either: a) cardiovascular death; b) nonfatal myocardial infarction (NFMI); or c) nonfatal (NF) stroke).*
- In our formal dispute resolution request letter from September 15, 2011, the confidence intervals were based on the 3-component composite endpoint and not on the broadened (b) (4) component composite.*

Sponsor/Consultants stated the following:

- [REDACTED] (b) (4)*

They also stated that if choosing to use the (b) (4) component composite endpoint, including [REDACTED] (b) (4) as the primary study endpoint, it is understood that we will assess the contribution of the individual components to the overall findings. If there are favorable trends with [REDACTED] (b) (4) but the more conservative MACE endpoints (CV death, NFMI, NF stroke) trend adversely, it is unlikely that we would

believe there was adequate evidence of cardiovascular safety. The sponsor understood that they assumed this risk by using the broadened endpoint.

- *They planned to use the FDA/CDISC draft recommendation for standardized definitions for cardiovascular outcomes trials and that these definitions would be included in the final protocol.*
- *They would submit the data from an analysis of multiple trials looking at the hazard ratio for (b) (4) vs the 3-component composite to assess for consistent, concordant data that was estimated to occur in 48 of the 50 trials examined.*

We stated that we would be open to re-considering the (b) (4) component composite endpoint and encouraged them to submit whatever evidence they had to justify the addition of (b) (4) into the MACE endpoint for a non-inferiority trial.

PATIENT POPULATION

Sponsor Question 4: Inclusion criteria include BMI, waist circumference, age, and existence of CV disease or diabetes with additional risk factors. Does the Division agree in concept with the scope of these criteria?

FDA Preliminary Comment: Yes.

Meeting Discussion: We stated based on our experience with the diabetes trials, there are certain inclusion criteria that may be very helpful in achieving a study population that would have an underlying cardiovascular risk of approximately 1.5%. The recommended criteria include increased age, increased duration of diabetes, use of insulin in subjects with type 2 diabetes, and prior cardiovascular events.

In order to make some inference about the different risk populations and to make some comparison to the SCOUT trial, we would like the enrolled subjects to meet the following categories:

- *1/3 with a history of CVD (CAD/PAD) without DM*
- *1/3 with a history of CVD (CAD/PAD) with DM*
- *1/3 with a history of DM without CVD (CAD/PAD)*

Orexigen stated they would reevaluate this.

WEEK 16 ASSESSMENT TO CONTINUE TREATMENT

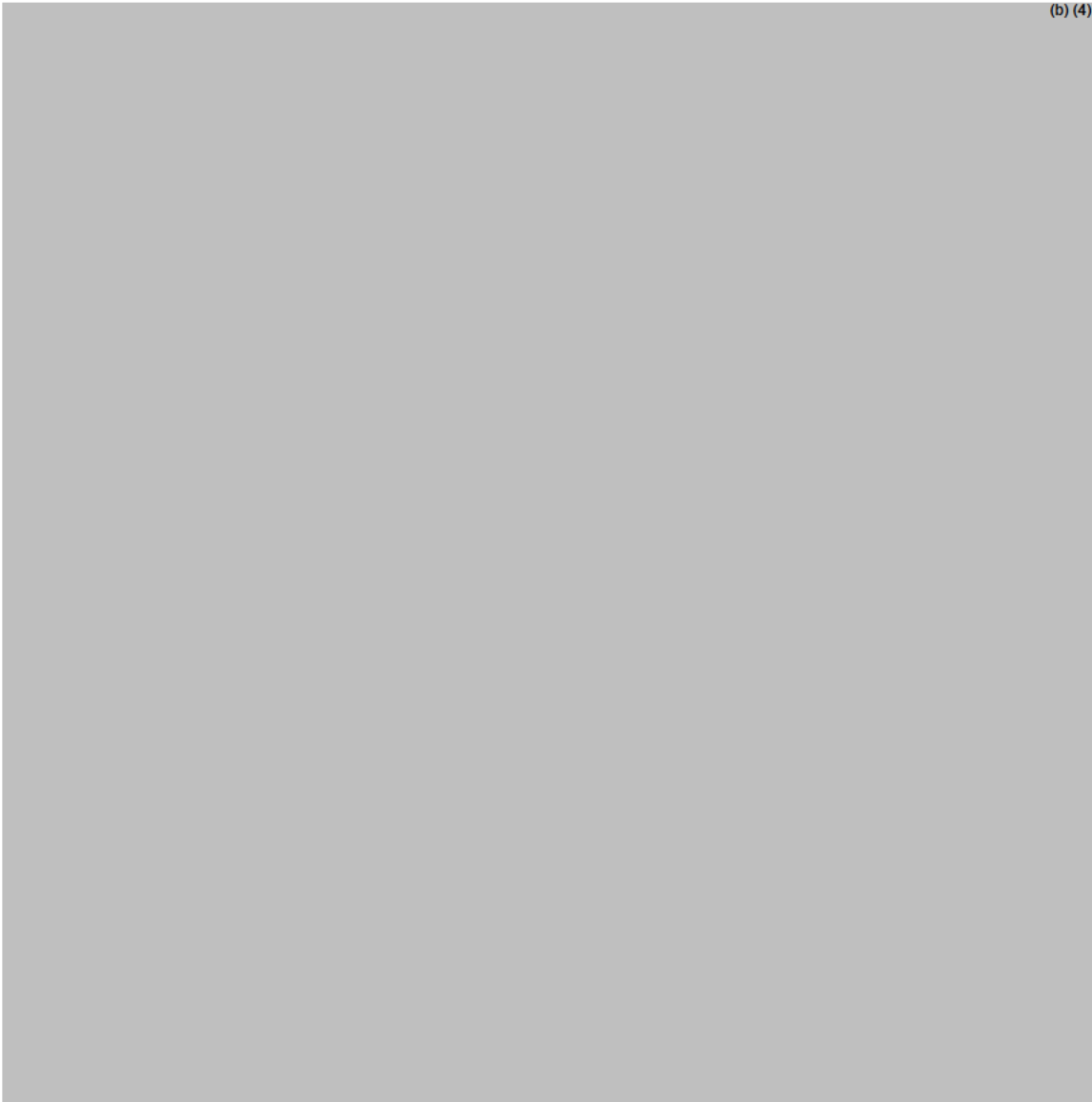
Sponsor Question 5: Does the Division agree with the approach for defining the Week 16 criteria to continue treatment, to support similar subject retention in the active and

placebo arms, while ensuring that subjects are losing weight on study without undue risk related to elevations in blood pressure?

FDA Preliminary Comment: We understand that your proposal to use a 2% weight loss threshold will help to minimize disproportionate loss of placebo-treated subjects who might not achieve (b) (4) body weight loss by Week 16. (b) (4)

(b) (4) **We have no objection to the use a 2% weight loss threshold as one of the criteria for continuing treatment at Week 16.**

Meeting Discussion: None



(b) (4)

(b) (4)

Meeting Discussion: None

ASSESSMENT OF BODY WEIGHT

Sponsor Question 10: Will the Agency continue to hold the view that Contrave efficacy has been established in the Phase 3 program irrespective of the outcome from the upcoming Advisory Committee meeting or other changes to weight management product guidance?

FDA: We reiterate that the outcome of the upcoming obesity Advisory Committee will not alter the agreements made with this Contrave CVOT and we will honor the advice provided for the Contrave CVOT.

We concur that Contrave has satisfied the categorical weight loss efficacy criterion, as described in the 2007 draft guidance for weight management products.

When we are reviewing the CVOT for Contrave, we will review all the data from the trial, both efficacy and safety data, but our focus will be on the safety data. We are not asking you to re-establish that you have satisfied the efficacy criteria as this trial is primarily designed as a safety trial. However, it would be concerning if Contrave was found to significantly increase CV risk but achieved little to no weight loss over the course of the trial. As we noted in our 15 September 2011 response to your formal dispute resolution request, and as stated in the diabetes guidance, we will consider the point estimate as part of our review of the data. The totality of the data will factor into the overall benefit-risk assessment of Contrave, as it does in any clinical trial that we review.

Meeting Discussion: None

Additional Comments:

- *Orexigen stated that using the ^(b)₍₄₎ component composite endpoint, they hope to begin enrollment in the second quarter of 2012 with an estimate of an interim analysis in mid-2014 and completion of the trial in 2017.*
- *Orexigen plans on submitting the protocol in December and the Data Monitoring Committee Charter in January along with a discussion on how the blind will be maintained throughout the trial.*
- *Orexigen has not decided if they will submit the protocol as a Special protocol assessment (SPA) or not.*
- *We stated that once we received the protocol, we would respond in four to six weeks.*

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit the data from an analysis of multiple trials looking at the hazard ratio for (b) (4) vs the 3-component composite to assess for consistent, concordant data that was estimated to occur in 48 of the 50 trials examined.	Sponsor	Two weeks from the time of issue of this correspondence.

5.0 ATTACHMENTS: see slides below

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/s/

MEGHNA M JAIRATH
12/12/2011

10-15-12



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 200063

DISPUTE APPEAL – DENIED

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines, Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone hydrochloride and bupropion hydrochloride extended release tablets).

I refer to your request for formal dispute resolution, dated and received on August 7, 2012 to the Center for Drug Evaluation and Research (CDER). The request for formal dispute resolution concerns the pre-approval requirement cited in the January 31, 2011, complete response (CR) letter, for a pre-approval randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with Contrave does not adversely affect the drug's benefit-risk profile. I refer to your formal dispute resolution request, received on June 8, 2011, to the Office of Drug Evaluation (ODE II), and the denial of the appeal by Dr. Curtis Rosebraugh, Director, ODE II on July 7, 2011. I also refer to your formal dispute resolution request, received on July 14, 2011, to the Office of New Drugs (OND), and the denial of the appeal by Dr. John Jenkins, Director, OND on September 15, 2011. Finally, I refer to the meeting held between FDA and Orexigen on September 6, 2012, where the issues raised in your request for formal dispute resolution were discussed, and to the additional requested information received on September 14, 2012.

I have carefully reviewed the materials you submitted in support of your appeal, the reviews and decision memoranda prepared by FDA staff, the CR letter, Dr. Rosebraugh's and Dr. Jenkins' appeal denied letters, and other pertinent material (e.g. material and transcripts from the December 7, 2010, Endocrinologic and Metabolic Drugs Advisory Committee meeting, reviews and action letters for other weight management drugs). I have also consulted with staff in Division of Metabolism and Endocrinology Products (DMEP), ODE II, with Dr. Lisa LaVange (Director, Office of Biostatistics), with Dr. Robert Temple (Deputy Center Director for Clinical Sciences), and with Dr. Gerald Dalpan (Director, Office of Surveillance and Epidemiology).

I have completed my review of your request for formal dispute resolution and deny your appeal which requested that I concur with your position that "... CONTRAVE is approvable on the basis of existing data with labeling (including a Medication Guide) that properly alerts prescribers and patients to the drug's blood pressure effects, together with a requirement to complete the ongoing CVOT as a post-marketing requirement with an aggressive and very near term deadline for results." As I discuss below

I do, however, agree with your suggestion regarding additional steps that should be explored fully to most efficiently make use of the data from the ongoing study of Contrave.

To summarize my conclusions and recommendations (these points will be discussed in the paragraphs following):

1. I concur with the previous FDA finding that Contrave is not being held to a different standard from that used to approve Belviq and Qsymia¹. There is greater uncertainty about the cardiovascular safety of Contrave when used in its intended population than there is for either Belviq or Qsymia, and this greater uncertainty is not offset by any unique advantage or other mitigating factor.
2. I concur with the previous FDA finding that there is sufficient uncertainty about the long-term cardiovascular safety of Contrave that it cannot be approved with labeling as you propose while awaiting the results of the ongoing cardiovascular outcomes trial (CVOT). I also conclude that while there are other labeling strategies with the potential to allow for the approval of Contrave before the availability of any results from the ongoing cardiovascular safety trial, those necessary strategies are not acceptable to you².
3. I concur with the previous FDA findings that the use of Risk Evaluation and Mitigation Strategy (REMS) to address this additional uncertainty is not an appropriate tool to use to support the approval of Contrave without additional safety data.
4. I strongly support the conversations you and the Division have had concerning innovative ways to make use of the interim data from the ongoing cardiovascular safety trial, as well as the proposal you made for additional discussions to further facilitate the review of Contrave in anticipation of those results³.

Approval Standard for Contrave and Other Weight Loss Drugs and Cardiovascular Safety of Contrave

As Dr. Jenkins discussed⁴, our approach to the cardiovascular safety of drugs with sympathomimetic effects is influenced by our past experiences with other drugs. Unfortunately, we do not know exactly which manifestation of sympathomimetic effects are most critical, nor do we have a quantitative link between them and long-term clinical outcomes. As a result, I do not know how to rank drugs with these effects by looking at the short-term measures of the sympathomimetic effect (e.g., heart rate, blood pressure, measures of vascular responsiveness, pulse pressure) to predict their long-term clinical effects measured in randomized trials. However, as we discussed in our meeting and Dr. Jenkins summarized, drugs with this pharmacology need to be carefully assessed so that their overall risks and benefits can be described accurately. In this sense, both Qsymia and Contrave are sympathomimetic drugs, like sibutramine, and bear special attention when used chronically.

Separate from this uncertainty, however, Contrave has one effect that has been clearly linked to negative long-term consequences: chronic elevation in blood pressure (BP) above the levels seen in patients treated with placebo. As we discussed, we have clear instances where drugs (or dietary supplements) that cause modest sustained elevations in blood pressure have negative cardiovascular effects⁵. Regardless of whether this occurs as a part of a larger sympathomimetic effect (e.g., ephedra)

¹ Lorcaserin and phentermine/extended-release topiramate respectively.

² In an email to me dated October 2, 2012.

³ In an email to me dated September 11, 2012.

⁴ In his letter dated September 15, 2011.

⁵ In the case of ephedra we have spontaneous reports of adverse cardiovascular effects and not controlled trial data.

or by other pharmacology (e.g., COX-2 inhibitors), this is a property that raises additional concern. This concern must be offset by either additional data (e.g., the long-term cardiovascular safety trial) or by other means of managing the overall balance of risk and benefit for its use.

This effect to increase BP chronically is not shared by either Belviq or Qsymia, and they have no other identified cardiovascular effects that raise safety concerns to a similar degree as an effect to raise BP chronically⁶.

Given the additional uncertainty about the long-term cardiovascular safety of Contrave, I conclude that it cannot be approved with labeling as you propose. Further, I understand and agree with Dr. Jenkins and his overall conclusion that Contrave was treated fairly, consistent with how we have treated other recent obesity drug applications.

Other Alternate Risk Mitigation Tools: Potential Use of REMS Too Support Contrave Approval

One strategy you proposed during previous submissions was the use of a REMS to support Contrave approval in advance of the data from the CVOT⁷. Here, I concur with what Dr. Jenkins said in his appeal. Given the pace of the ongoing CVOT trial and the burden such a REMS would impose on the healthcare system for the level of the additional uncertainty about the cardiovascular safety for Contrave, use of a REMS as you have previously proposed would not be appropriate.

Alternate Labeling Tools to Support Contrave Approval

As you suggest, labeling is the cornerstone of risk management. In this case, I do believe a labeling strategy exists to limit the use of Contrave to those individuals who have failed to respond to the other approved weight loss drugs⁸, and that such a strategy could be employed to market Contrave in advance of the data from the CVOT⁹. Having raised this as an option, I also recognize that you believe such a labeling is not something you could support.

I do not support less restrictive labeling approaches to limiting the use of Contrave, including the approach you suggested (labeling to recommend against the use of Contrave except by individuals who lose weight while taking it but otherwise grant it an indication similar to the labels for Qsymia and Belviq)¹⁰. While uncertainty remains about the precise impact of labeling on decision-making by physicians, this type of labeling seems unlikely to me to achieve the goal of limiting Contrave use to individuals without other pharmacologic options. I am also concerned that such labeling might inadvertently suggest its use in a population at higher cardiovascular risk (the group I have particular concerns about its use in advance of the long-term cardiovascular data).

⁶ I am aware of the data on heart rate for Qsymia. While drug effects on heart rate have been observed and reported they have not been the basis of regulatory actions in the way chronic elevations in BP have.

⁷ This was not part of your most recent proposal to me but was discussed in previous appeals.

⁸ The approved therapies have different pharmacologic properties from Contrave, so that there is a rationale for believing that Contrave will have efficacy by testing its effects on weight loss in patients who have failed those drugs. I note that this hypothesis has not been rigorously tested by giving Contrave to 'treatment failures' to Qsymia or Belviq.

⁹ While the specifics of such labeling were not discussed, I believe it would require language indicating the use of Contrave only in individuals who have tried and failed to respond to other approved weight loss drugs. Additional language in labeling to provide prescribers with information about the increased level of uncertainty about its long-term cardiovascular effects relative to those drugs and to help, individuals and their physicians make an informed decision about using Contrave would also have been important.

¹⁰ Discussed in your email dated September 11, 2010.

Recommendations for Next Steps

In the absence of an acceptable pathway to approval utilizing labeling, you have suggested another pathway for the review of Contrave in lieu of waiting for the interim results from the CVOT to resubmit your application¹¹. You and OND have already begun important work to most efficiently use the data collected as a part of the ongoing CVOT. The additional step you suggest, to plan for a submission to be under review at the time of the interim analysis in order to be as prepared as possible to act soon afterwards, represents a further refinement of that work. While there are procedural issues to be addressed, I am highly supportive of discussions with CDER about this approach in this critical area of public health need. Should you decide to pursue this pathway, I look forward to hearing about the results of those discussions through Dr. Jenkins.

I would be happy to meet with you to discuss my decision and recommendations with you further if that would be valuable to you. Questions regarding next steps as described in this letter should be directed to Meghna Jairath, Pharm D., Regulatory Health Project Manager, DMEP, (301)796-4267.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA). The appeal should be sent through the Office of the Ombudsman, FDA, (301) 796-8530 (email ombuds@oc.fda.gov), with a copy to the NDA administrative file as an amendment and a copy to Amy Bertha, CDER's Formal Dispute Resolution Project Manager. If you have any questions about the formal dispute process, please contact Amy Bertha at (301)796-1647.

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Deputy Director for Regulatory Programs
Center for Drug Evaluation and Research
Food and Drug Administration

¹¹ Discussed in your email dated September 11, 2012.

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/s/

DOUGLAS C THROCKMORTON
10/15/2012

10-12-19



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200063

MEETING MINUTES

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, MD
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under-section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 6, 2012. The purpose of the meeting was to discuss the issues raised in your request for formal dispute resolution dated August 7, 2012.

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) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: September 6, 2012, 9:00 - 10:30am EST
Meeting Location: White Oak Campus, Building 21, Rm 1537

Application Number: NDA 200063
Product Name: Naltrexone hydrochloride and bupropion hydrochloride extended release tablets

Sponsor/Applicant Name: Orexigen Therapeutics, Inc.

Meeting Chair: Doug Throckmorton, M.D.
Meeting Recorder: Amy Bertha

FDA ATTENDEES

Center for Drug Evaluation and Research

Douglas Throckmorton, M.D. Deputy Center Director for Regulatory Programs
Robert Temple, M.D. Deputy Center Director for Clinical Sciences

Office of New Drugs

John Jenkins, M.D. Office Director
Amy Bertha Team Leader
Khushboo Sharma, M.B.A., RAC Sr. Regulatory Health Project Manager,

Office of Drug Evaluation II, Office of New Drugs

Curtis Rosebraugh, M.D., M.P.H. Office Director
Christine Nguyen, M.D. Acting Deputy Office Director
Eric Colman, M.D. Deputy Division Director, Division of Metabolism and Endocrinology Products
Julie Golden, M.D. Medical Officer, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II
Eileen Craig, M.D. Medical Officer, Division of Metabolism and Endocrinology Products
Mary Roberts, M.D. Medical Officer, Division of Metabolism and Endocrinology Products

Office of Biostatistics, Office of Translational Sciences

Lisa LaVange, M.D. Director
Aloka Chakravarty, Ph.D. Division Director, Division of Biometrics VII
Thomas Permutt, Ph.D. Division Director, Division of Biometrics II
Janice Derr, Ph.D. Statistical Reviewer, Division of Biometrics II, Office of Biostatistics

SPONSOR ATTENDEES

Michael Narachi Chief Executive Officer, Orexigen Therapeutics
Preston Klassen Senior Vice President, Global Development, Orexigen Therapeutics
Heather Turner Senior Vice President, General Counsel, Orexigen Therapeutics
Dawn Viveash Senior Vice President, Global Regulatory Affairs, Orexigen

Kristin Taylor	Therapeutics
Tom Bicsak	Senior Director, Clinical Development, Orexigen Therapeutics
Teri Johnson	Senior Director, Regulatory Affairs, Orexigen Therapeutics
	Director Program Management and Strategic Operations, Orexigen Therapeutics
Collen Burns	Director, Biostatistics, Orexigen Therapeutics
Mick Roebel	Global Regulatory Affairs, Therapeutic Area Head, Takeda
Eckhard Leife	Takeda
Thomas Strack	Pharma Products Division Therapeutic Area Head, Takeda
Josephine Torrente	Regulatory Consultant and Counsel, Hyman Phelps & McNamara, P.C

BACKGROUND

Orexigen submitted a formal dispute resolution request to the Office of Drug Evaluation II (ODE II) on June 8, 2011, concerning the complete response action taken on January 31, 2011, specifically the preapproval requirement for a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. Dr. Curtis Rosebraugh, Director, ODE II denied the appeal on July 7, 2011. Orexigen submitted a request for formal dispute resolution to the Office of New Drugs (OND) on July 14, 2011. Dr. John Jenkins, Director, OND denied the appeal on September 15, 2011. Orexigen submitted request for formal dispute resolution to the Center for Drug Evaluation and Research on August 7, 2012. Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs, is the deciding authority. In Orexigen's August 7, 2012, dispute resolution submission, the company requested a meeting with the deciding official before he rendered his decision on this matter. The meeting was granted and took place on September 6, 2012.

MEETING OBJECTIVES

The objective of this meeting was to discuss the issues surrounding the appeal.

DISCUSSION

Orexigen had a brief presentation to open the meeting, and then FDA and Orexigen discussed the following issues:

- The benefit/risk profile of several weight management drugs were compared, specifically, sibutramine, Qsymia, Belviq, and Contrave. Some of the safety aspects of each drug, i.e., the short term and long term effects on blood pressure and heart rate increases were discussed. The efficacy aspects of the various drugs, i.e., weight loss, were also included in the discussion. The different pre- and post-approval commitments and requirements between the drugs, specifically whether the cardiovascular outcomes trial (CVOT) be conducted pre- or post-approval, were also discussed.
- How the landscape of the weigh management class of drugs has changed since the approvals of Qsymia and Belviq, and how Contrave would fit into this environment.
- From a regulatory perspective how drugs, in this therapeutic area and other therapeutic areas, with a negative blood pressure and/or heart rate effects are treated at the FDA, and how these negative effects could be managed through labeling. For the weight management class of drugs, how the general benefit of weight reduction is considered in approval decisions.
- Possible path forward approaches were discussed, including, how restrictions on use would affect the overall benefit/risk profile of Contrave, and risk management approaches for Contrave, noting that the current formal appeal did not include a risk management proposal.

DECISION (AGREEMENTS) REACHED:

This meeting was not conducted with the expectation that decisions would be made or agreements reached at the meeting. The issues discussed will be taken into consideration when reaching a decision regarding the formal dispute resolution request which will be made in 30 days from the meeting date.

ACTION ITEMS:

- Orexigen to provide additional information regarding alternative paths forward for resolution.

ATTACHMENTS/HANDOUTS:

Slides from Orexigen Presentation

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/s/

AMY E BERTHA
10/12/2012

11-15-11

Medical Officer Review
Division of Metabolism and Endocrinology Products (HFD-510)

IND: NDA 200063 (IND 68,858)

Serial No.: Meeting materials for 16 Nov 2011 meeting

Drug Name: Naltrexone/Bupropion (Contrave®)

Sponsor: Orexigen

Proposed Indication: Obesity

Date of Submission: 1 November 2011

Medical Reviewer: Eileen Craig, MD
Statistical reviewer: Xiao Ding, PhD

Medical Team Leader: Eric Colman, MD
Statistical Team Leader: Mat Soukup, PhD

Review Date: 15 November 2011

Internal Meeting: Thur 11/10/11 3pm-4pm Bldg 22- Room 3270
Industry Meeting: Wed 11/16/11 10a-11:30a Bldg 22- Room 1415

The purpose of this submission is to provide the draft protocol for the proposed Cardiovascular Outcomes Trial (CVOT) along with an accompanying Briefing Document to support discussion at the Type A meeting scheduled for 16 November 2011. The intent of the Type A meeting is to discuss the design of a CVOT intended to address the Approval Deficiency in the Complete Response Letter (CRL) for Contrave NDA 200063.

In the 15 September 2011 response to Orexigen's formal dispute resolution request (FDRR), the Office of New Drugs (OND) outlined detailed elements of a CVOT design that would meet the requirements set forth in the CRL:

1. The trial should enroll a population of overweight and obese patients with an estimated background annual risk of MACE of 1.0-1.5%. There should be a reasonable representation of patients at higher risk, such as patients who have a history of cardiovascular disease.
2. The trial should follow patients long enough to allow an assessment of the long-term safety; i.e., 2-3 years.

3. We do not object to your proposal to stop drug therapy in patients who are not experiencing some pre-specified level of weight loss, but all patients should continue to be followed once off study drug for CV events.
4. With regard to the criteria for the interim and final analyses, we agree that the intent-to-treat analysis will be considered primary. We will also look at the per-protocol analysis, but the trial does not need to be powered based on that analysis.
5. We believe the criteria for interpretation of the trial should be similar to those that are applied to diabetes drugs; albeit with some differences to account for the expected lower background risk of CV events. For a population with a background risk of 1.0-1.5%, this would translate to a final analysis that excludes a hazard ratio of 1.4 (upper bound of the 95% CI). The interim analysis should exclude a hazard ratio of 2.0 (upper bound of the 95% CI). In both cases, we are no longer requiring specific power calculations based on the observed point estimate; however, as stated in the diabetes guidance, we will consider the point estimate as part of our review of the data.
6. Based on calculations performed by our statisticians, the final analysis will require approximately 371 events and the interim analysis will require approximately 87 events when powering the study with 90% power and under the parameter assumption that the hazard ratio is 1.0.
7. If the interim analysis meets the specified criteria to exclude an unacceptable increased CV risk, the drug could be approved (barring any unexpected new safety signals), most likely with a REMS, while the trial is completed.

The following table provides sample size calculations using 90% power under the assumption that the true hazard ratio is 1.

Event Rate (per 100 subject years)	Relative Risk									
	1.4	1.5	1.6	1.8	1.9	2.0	2.2	3.0	3.4	
0.5	RD	0.20%	0.25%	0.30%	0.40%	0.45%	0.50%	0.60%	1.00%	1.20%
	EE	2.0	2.5	3.0	4.0	4.5	5.0	6.0	10.0	12.0
	Events	371	255	190	121	102	87	67	34	28
	PY	74200	51000	38000	24200	20400	17400	13400	6800	5600
	PE	1.14	1.17	1.20	1.26	1.29	1.32	1.37	1.54	1.62
1.0	RD	0.4%	0.5%	0.6%	0.8%	0.9%	1.0%	1.2%	2.0%	2.4%
	EE	4.0	5.0	6.0	8.0	9.0	10	12.0	20.0	24.0
	Events	371	255	190	121	102	87	67	34	28
	PY	37100	25500	19000	12100	10200	8700	6700	3400	2800
	PE	1.14	1.17	1.20	1.26	1.29	1.32	1.37	1.54	1.62
1.5	RD	0.6%	0.75%	0.9%	1.2%	1.35%	1.5%	1.8%	3.0%	3.6%
	EE	6.0	7.5	9.0	12.0	13.5	15	18.0	30.0	36.0
	Events	371	255	190	121	102	87	67	34	28
	PY	24733	17000	12666	8066	6800	5800	4466	2266	1866
	PE	1.14	1.17	1.20	1.26	1.29	1.32	1.37	1.54	1.62

RD = Risk Difference (Rate Contrace minus Rate Control)
 EE = Excess Events (Events Contrace minus Events Control)
 Events = Number of events required for 90% power
 PY = Patient years need to observe required events
 PE = Maximum value of point estimate for RR in order to meet upper bound threshold.

Note

- Sample size calculations (i.e. number of events needed) are based upon an ITT analysis population

The protocol originally proposed by Orexigen has now been modified to incorporate the elements identified by OND, and it is this revised version that Orexigen is seeking alignment on with the Review Division, prior to submitting it through the Contrace IND under a Special Protocol Assessment (SPA).

See Appendix A for the protocol synopsis.

Orexigen's Questions:

1. Does the Division agree in general with the proposed CV outcomes trial design?

FDA:

Primary endpoint: Please refer to our comments for Question #3 regarding the primary composite endpoint. We believe the appropriate primary endpoint for this non-inferiority trial is MACE defined as cardiovascular (CV) death, nonfatal myocardial infarction (NFMI), and nonfatal stroke.

(b) (4)

(b) (4)

Secondary endpoint:

(b) (4)

analyses. This analysis may only be considered as exploratory as it will be based on

(b) (4)

2. Does the Division agree with the following specific aspects of the proposed CV outcomes trial as detailed in the protocol:

a) Study design and schema?

FDA: [Statistical team preliminary comment]

No. A more thorough description of the following items needs to be provided in a revised protocol.

1. Information on the randomization procedures is not sufficiently addressed in the current protocol. The following information should be provided in your revised protocol.

- **Process of randomization:** Describe how randomization will be performed (e.g. whether a centralized system such as an interactive voice response system will be used). In addition state whether a simple stratification procedure will be used or if block randomization will be provided.
- **Stratification:** In section 9.9, the sponsor proposed that baseline CV risk group will be used as a stratification factor for the randomization. The sponsor should clarify whether any other stratification factors will be incorporated into the randomization scheme (e.g. site or any of the covariates for which the primary analysis will be adjusted – sex, age).

2. Since the proposed trial design includes both a single-blinded lead-in phase and a double-blinded treatment phase along with a proposal to include multiple interim analyses and multiple hypotheses testing, it is very important to specify how the blindness will be maintained throughout the whole trial. This is critical to maintain the quality and integrity of the proposed CV outcome trial. The following items should be addressed in regards to study blinding.

- Provide a finalized DMC charter.
- Provide details for when to break the blindness of treatment assignment and when the database will be locked for the first stage analysis to rule out the non-inferiority margin of 2.0.
- Provide a description of measures planned to be taken in order to maintain the blindness after conducting the first stage analysis to rule out NI margin of 2.0 and continue the trial for the final stage analysis to rule out NI margin of 1.4.

b) Approach to data collection, including handling of MACE endpoints, blood pressure data, and proposed efficacy and safety measures?

FDA: In general, yes. We note that laboratory assessments will only be done at the beginning of the trial and data on concomitant medications will only be collected at the beginning and end of the trial. This will limit the ability to assess for changes in medications for hypertension or diabetes and we will not be able to assess for changes in HbA1c or lipids during the trial.

We also note that routine safety data collection will be limited to adverse events leading to discontinuation of study medication and SAEs. Information on in-utero exposures and pregnancy outcomes will be collected. Safety data will be reviewed on an ongoing basis by an independent Data Monitoring Committee (DMC).

When submitting the protocol for the cardiovascular safety outcomes trial, please provide:

- **Definitions for all primary , secondary and other endpoints and events of special interest**
- **Case Report Form for capturing cardiovascular events**
- **Clinical Endpoints Committee (CEC) Charter, including algorithms to be used for cardiovascular endpoint events**
- **Statistical Analysis Plan (SAP) or detailed statistical section of the study protocol**

c) Sample size?

FDA: Based on the assumptions provided in the protocol, the proposed sample size is reasonable.

What percentage of the 300 centers for the trial will be in the US?

What attempt will be made for inclusion of more non-white individuals into the CVOT?

d) Statistical analysis and testing strategy?

FDA: [Statistical team preliminary comment]

1. It is acceptable to include covariates other than the treatment (sex, age, baseline CV risk group) in the primary analysis model. However, please provide clarifications on the following points.

- **For age, please clarify whether it will be included in the Cox regression model as a continuous variable or a categorical variable. If**

age categories will be used, definition of the categories should be pre-specified in the protocol.

- For baseline CV risk group, please clarify what is the meaning of “each potentially with additional risk factors” (draft protocol page 36 Section 9.4.7). The total number of risk groups (i.e. levels of baseline CV risk), as well as a detailed definition of each group, should be pre-specified in the protocol.
- Other covariates to be included, in addition to age, are gender and race.
- Cox regression model with only one covariate of treatment should also be conducted as a sensitivity analysis. Unlike the case of regular linear regression model, to include more covariates in a Cox regression model won't always result in treatment effect estimate with more precision. Furthermore, for the first stage analysis to rule out NI margin of 2.0, the Cox regression model will be based on no more than 88 events. With the relatively small number of events, the impact of including several additional covariates (sex, age, baseline CV risk groups) in the Cox regression model need to be assessed.

2. Given the results from the primary Cox regression model, it is not clear how the sponsor plans to test each of the 3 null hypotheses (H01, H02, H03). Whether two-sided confidence interval or one-sided interval will be used for the hypotheses testing should be specified in your revised protocol.

3. The sponsor proposed to utilize a (b) (4) to ensure strong control of the family-wise type 1 error rate. It should be noted that the (b) (4) is normally applied to address multiplicity issues arising in the analysis of clinical trials with multiple endpoints and/or multiple dose levels. It is not commonly used when interim analyses are involved. In this case, the proposed testing strategy should be viewed as a sequential testing strategy rather than a (b) (4). In the trial proposed, we consider testing to be conducted at two stages: Stage 1 corresponds to ruling out a HR of 2.0 (H01) and Stage 2 corresponds to ruling out a HR of 1.4 (H02) (b) (4)

4. It is statistically acceptable to use the full alpha to sequentially test the 3 null hypotheses in the order of H01→H02→H03. The proposed testing strategy should be able to correctly control the overall type 1 error rate if any of the following three events occur.

- A. When the true hazard ratio for NB32 relative to placebo is ≥ 2.0 , falsely approve NB32 at the time of first stage analysis
- B. When the true hazard ratio for NB32 relative to placebo is ≥ 1.4 , falsely conclude NB32 is safe enough to stay on the market at the time of final stage analysis.

In other words, the probability of event A, B, or C occurs is less than 2.5%. Furthermore, the probability of any two or even all three of the three events occur is also controlled to be less than 2.5%.

It should be noted that at Stage 1 (i.e. ruling out a HR of 2.0) for which the product will be evaluated for approval, there is no guarantee that at Stage 2 the trial will be able to rule out HR of 1.4 based upon a sequential testing procedure. Determination of the trial to meet study objectives at Stage 2 based on data from Stage 1 should be evaluated by calculating conditional power or through simulation. Determination of approvability at Stage 1 will ultimately be a review issue.

PRIMARY ENDPOINT

In order to maximize accrual of MACE in this trial, Orexigen proposes to use a composite endpoint that includes events of (b) (4) as the primary study endpoint. This is reflected in the primary objective as stated in the draft protocol:

To assess 32 mg naltrexone sustained-release (SR)/360 mg bupropion SR (NB32) compared to placebo on the occurrence of MACE, including cardiovascular death, nonfatal myocardial infarction, (b) (4) or nonfatal stroke in overweight and obese subjects.

Orexigen believes that inclusion of (b) (4) as one of the components of the primary composite endpoint is consistent with current Agency thinking regarding the breadth of objective outcomes that can be used in assessing cardiovascular risk, e.g., for diabetes drugs as described in the 2008 FDA Guidance *Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The 2010 CDISC *Standardized Definitions for End Point Events in Cardiovascular Trials* criteria for (b) (4) (b) (4) would be employed in identifying angina events as MACE in this trial.

3. Does the Division agree with the use of a (b) (4) component composite endpoint, (b) (4) (b) (4) as the primary study endpoint?

Internal MO Comment: In previous correspondence, we had agreed with the sponsor's primary MACE endpoint of CV death, nonfatal MI, and nonfatal stroke. They now request to add in (b) (4) stating that this is consistent with the 12/2008 FDA Guidance *Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* which states

“Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.”

Looking at CV trials proposed for DM drugs, the primary composite endpoint always consists of CV death, NF MI, and NF stroke. However, some trials have allowed

(b) (4) IND (b) (4) IND (b) (4)
(b) (4) IND (b) (4)/albiglutide; IND (b) (4)/sitagliptin; (b) (4) and
(b) (4) I found one trial (IND (b) (4)/albiglutide) where the primary
composite endpoint (b) (4)
(4)

Because Orexigen’s trial is a non-inferiority trial, I would recommend a more strict MACE definition of CV death, NFMI, and NF stroke. “Softer” endpoints, such as revascularizations, hospitalization for unstable angina, and hospitalization for heart failure, are more subjective, can be challenging to define, and may differ depending on the local community standard of care. This variability of these more subjective endpoints can bias results towards showing no difference between treatments—which would be considered a ‘win’ in a non-inferiority trial and a ‘loss’ in a superiority trial. However, as (b) (4) has been allowed in the primary composite endpoint for non-inferiority DM trials, this makes the strict MACE definition somewhat inconsistent with what has been allowed for DM drug trials.

FDA: As we have stated in previous correspondence including the End-of-Review meeting and the Formal Dispute Resolution Requests, we believe that the appropriate MACE endpoint for this non-inferiority trial consists of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

“Softer” endpoints, such as revascularizations, hospitalization for unstable angina, and hospitalization for heart failure, are more subjective, can be challenging to define, and may differ depending on the local community standard of care. The variability of these more subjective endpoints can bias results towards showing no difference between treatment groups. We are aware that (b) (4). (b) (4) has been allowed in the primary composite endpoint for some non-inferiority CVOT of antidiabetic agents. However, we believe strict MACE should be the primary endpoint for the proposed Contrave non-inferiority CVOT.

PATIENT POPULATION

Orexigen is in the process of defining a study population that would have an underlying cardiovascular risk of approximately 1.0-1.5%. They have proposed in the draft protocol to include the following subjects:

- ≥50 years of age (women) or ≥45 years of age (men)
- Body mass index (BMI) ≥27 kg/m² and ≤50 kg/m²
- Waist circumference ≥88 cm (women) or ≥102 cm (men)
- Have a diagnosis of at least one of the following:

- Atherosclerotic vascular disease (including coronary disease and peripheral arterial disease, but excluding cerebrovascular disease)
- Type 2 diabetes mellitus requiring pharmacotherapy with at least 2 of the following 3 comorbidities: (1) hypertension (controlled with pharmacotherapy at <140/90 mm Hg); (2) dyslipidemia requiring pharmacotherapy; (3) current tobacco smoker.

Based on inclusion criteria used in recent cardiovascular trials in obesity (SCOUT, CRESCENDO), Orexigen believes that including older subjects with either diagnosed atherosclerotic vascular disease or type 2 diabetes with at least 2 additional comorbidities will result in a population with the intended underlying CV risk.

4. Inclusion criteria include BMI, waist circumference, age, and existence of CV disease or diabetes with additional risk factors. Does the Division agree in concept with the scope of these criteria?

Internal comment: The inclusion criteria used in SCOUT¹ and CRESCENDO² are listed in the footnotes and are consistent with the inclusion criteria for Contrave's CVOT.

FDA: Yes.

WEEK 16 ASSESSMENT TO CONTINUE TREATMENT

The CVOT will have an assessment of subject response at Week 16 to ascertain weight loss as well as potentially unacceptable increases in blood pressure. Specifically as stated in the draft protocol:

At Visit 6 (Week 16) there will be an assessment of weight loss and blood pressure changes relative to baseline observations. The target weight loss is $\geq 5\%$ with expected minimum weight loss at 16 weeks of $\geq 2\%$. Subjects should be discontinued from study medication at Week 16 if: they have not lost at least 2% of their body weight *or* they are experiencing sustained (b) (4) increases in blood pressure (systolic or diastolic) of ≥ 10 mm Hg (or other increases deemed clinically relevant by the Investigator). If the Investigator suspects that an elevated blood pressure measurement may be spurious, subjects should not be discontinued until the elevated measurement is reconfirmed.

¹ SCOUT inclusion criteria: M&W ≥ 55 yrs; BMI ≥ 27 but ≤ 45 or BMI ≥ 25 but < 27 and waist circ of ≥ 102 cm in men or 88cm in women; hx of CVD (CAD, stroke, PAD), DM with at least 1 CV RF (HTN, dyslipidemia, current smoking, or DM neuropathy), or both. Exclusion criteria were sx of heart failure greater than New York Heart Association functional class II, BP $>$ than 160/100 mm Hg, a HR $>$ 100 bpm, scheduled cardiac surgery or coronary angioplasty, or a weight loss of more than 3 kg within the previous 3 months.

² CRESCENDO: The entry criteria were: abdominal obesity defined as waist circumference $>$ 88 cm in women and 102 cm in men; age older than 55 years; and either documented coronary heart, cerebrovascular, or peripheral artery disease in the past 3 years, or at least two major CV RF. Documented coronary heart disease was defined as hx of MI, multivessel coronary artery disease by angiography, previous coronary intervention, or bypass grafting. Cerebrovascular disease was defined as ischaemic stroke or transient ischaemic attack with abnormal MRI or CT. Peripheral artery disease was documented by a history of intermittent claudication and either an abnormal ankle-brachial index or vascular procedure. Risk factors included type 2 DM, abdominal obesity and at least two additional factors of the metabolic syndrome, renal artery disease, advanced age (men > 65 years, women > 70 years), asymptomatic cerebrovascular or peripheral artery disease, and raised high-sensitivity C-reactive protein.

Using data from the Contrave Phase 3 program, Orexigen has estimated the percent of available subjects at Week 16 who would be removed from study medication based on categorical weight loss criteria ranging from 1% to 5% (and also accounting for removal due to increased blood pressure), as shown in Table 1 below:

Table 1: Estimated Percent of Subjects Removed From Study Medication at Week 16*

Weight Loss Cutoff	Placebo**	NB32**
≥1%	30	21
≥2%	38	24
≥3%	46	30
≥4%	54	35
≥5%	61	40

* Based on pooled data from the NB Phase 3 program Studies NB-302 (intensive behavior modification) and NB-304 (type 2 diabetes).
 ** Percentage of subjects not achieving the specified degree of weight loss and/or with at least two consecutive increases of ≥10 mm Hg in either systolic or diastolic blood pressure.

Orexigen contends that use of a 2% weight loss threshold (b) (4) is believed to be most appropriate to capture subjects who have reasonable early weight loss (and therefore are likely to continue to lose weight with continued treatment) while minimizing disproportionate loss of placebo-treated subjects who might not achieve (b) (4) body weight loss by Week 16. In order to maximize subject safety during the trial (and as intended in proposed labeling), subjects with sustained blood pressure increases of 10 mm Hg or more will be withdrawn. Investigators will have the discretion to withdraw subjects with smaller blood pressure elevations if they believe subjects are at risk, but will be encouraged to verify that blood pressure increases are not spurious. Assuming use of a 2% weight loss criterion at Week 16, Orexigen projects that subject retention rates across treatment groups will be reasonably comparable over the 4-year study duration, as shown in Table 2. The retention rates in Table 2 reflect the projected proportion of subjects who will remain on randomized study medication; all subjects will continue to be followed up even if discontinued from randomized study medication, until the end of study or planned maximum follow-up of 4 years.

Table 2: Projected Subject Cumulative Retention Rate (%)*

Time Point	Placebo	NB32
Week 16**	51	56
Year 1	39	48
Year 2	32	40
Year 3	28	36
Year 4	27	33

* Based on data from the NB Phase 3 program (through Week 52) and the SCOUT and CRESCENDO trials (beyond Week 52). Rates are based on randomized subjects at Baseline, after anticipated withdrawal rate of 7% during the 2-week lead-in period.

** Includes assumptions for withdrawals for any reason, not only failure to meet the 2% weight loss or blood pressure criteria.

5. Does the Division agree with the approach for defining the Week 16 criteria to continue treatment, to support similar subject retention in the active and placebo arms, while ensuring that subjects are losing weight on study without undue risk related to elevations in blood pressure?

FDA: We understand that your proposal to use a 2% weight loss threshold will help to minimize disproportionate loss of placebo-treated subjects who might not achieve (b) (4) body weight loss by Week 16.

We have no objection to the use a 2% weight loss threshold as one of the criteria for continuing treatment at Week 16.

(b) (4) **FOR THE PRIMARY**

ENDPOINT

A Data Monitoring Committee (DMC) will be formed prior to study initiation and will have as its primary objective the monitoring of subject safety. As part of its role, the DMC will look at accumulating interim data on a periodic basis. It is possible that in its role, the DMC may advise the Executive Steering Committee and the Sponsor to stop the trial based on its review of the accruing data due to an indication of either clear benefit or harm to subjects participating in the study. The DMC may also examine whether or not the margins of 2.0 and 1.4 can be ruled out using (b) (4)

(b) (4)

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ASSESSMENT OF BODY WEIGHT

In the End of Review Meeting minutes issued by the Division on 27 June 2011, Orexigen notes that:

“...the data submitted in the NDA satisfy the categorical weight loss efficacy criterion, as described in the 2007 draft guidance for weight management products. If however, data from the CV safety trial indicated a significant loss of weight-loss efficacy in Contrave versus placebo-treated subjects with treatment beyond one year, we may factor this information into the overall benefit-risk assessment of Contrave.”

Furthermore, the 15 September 2011 Dispute Appeal response from OND to Orexigen states the following:

“...Contrave has met at least one of the criteria for efficacy stated in the Guidance is necessary to support approval...” *and*

“While we still plan to convene a public advisory committee meeting to discuss topics related to obesity drug development early next year, that meeting will not impact on the advice provided in this letter and the Agency will honor the advice provided.”

Orexigen requests reassurance from the Agency that planned, near-term Agency actions (e.g., outcome of upcoming obesity Advisory Committees and revision/issuance of revised obesity FDA Guidance) will not call into question the adequacy for approval of the efficacy of Contrave demonstrated in the Phase 3 program.

10. Will the Agency continue to hold the view that Contrave efficacy has been established in the Phase 3 program irrespective of the outcome from the upcoming Advisory Committee meeting or other changes to weight management product guidance?

FDA: We reiterate that the outcome of the upcoming obesity Advisory Committee will not alter the agreements made with this Contrave CVOT and we will honor the advice provided for the Contrave CVOT.

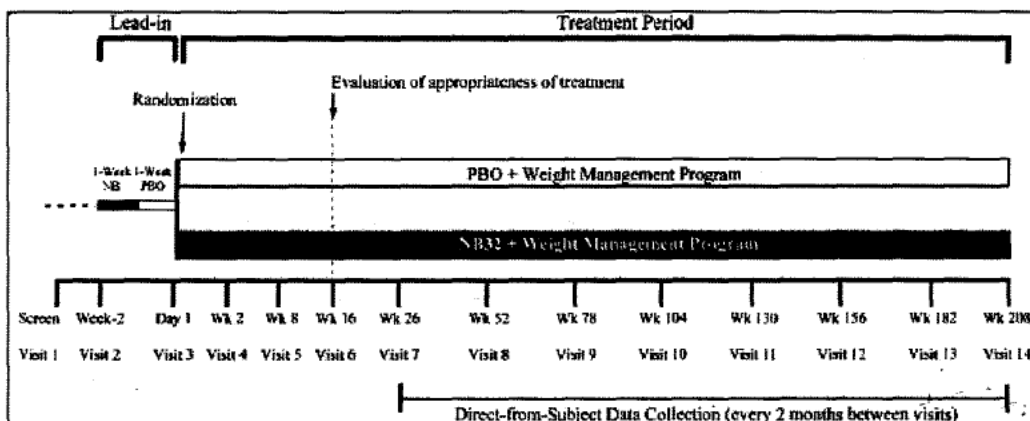
We concur that Contrave has satisfied the categorical weight loss efficacy criterion, as described in the 2007 draft guidance for weight management products.

When we are reviewing the CVOT for Contrave, we will review all the data from the trial, both efficacy and safety data, but our focus will be on the safety data. We are not asking you to re-establish that you have satisfied the efficacy criteria as this trial is primarily designed as a safety trial. However, it would be concerning if Contrave was found to significantly increase CV risk but achieved little to no weight loss over the course of the trial. As we noted in our 15 September 2011 response to your formal dispute resolution request, and as stated in the diabetes guidance, we will consider the point estimate as part of our review of the data. The totality of the data will factor into the overall benefit-risk assessment of Contrave, as it does in any clinical trial that we review.

APPENDIX A

TITLE A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Occurrence of Major Adverse Cardiovascular Events (MACE) in Overweight and Obese Subjects Receiving Naltrexone SR/Bupropion SR
PROTOCOL NUMBER NB-CVOT
PHASE Phase 3b
PRIMARY OBJECTIVE To assess 32 mg naltrexone sustained-release (SR)/360 mg bupropion SR (NB32) compared to placebo on the occurrence of MACE, including cardiovascular death, nonfatal myocardial infarction, (b) (4) (b) (4) or nonfatal stroke in overweight and obese subjects.
SECONDARY OBJECTIVES - To assess NB32 compared to placebo on the occurrence of each of the components of the primary endpoint in overweight and obese subjects. (b) (4)
OTHER OBJECTIVES - To assess the effect of NB32 on: - the occurrence of all cause mortality - the occurrence of coronary revascularization procedures - change in body weight - changes in systolic and diastolic blood pressure
STUDY DESIGN - This is a Phase 3b, multicenter, randomized, double-blind, placebo-controlled study to assess the occurrence of MACE in overweight and obese subjects receiving NB32. - Approximately 9,876 subjects will be enrolled into a single-blind lead-in period to help identify subjects who do not tolerate treatment with NB well or who exhibit other characteristics predictive of lack of compliance, with 1 week of active study medication (1 tablet per day) followed by 1 week of placebo (1 tablet per day). Eligible subjects will subsequently be randomly assigned to treatment with either NB32 or placebo in a 1:1 ratio. The duration of the randomized treatment period (or subject follow-up period for those who discontinue study medication early) is estimated to be between 2-4 years for most subjects. - Subject enrollment will consist of one cohort enrolled in two stages. During the first stage approximately 6,834 subjects will be enrolled in order to support accrual of sufficient events in randomized subjects for the interim analysis. The second stage will enroll approximately 3,042 subjects to complete the study enrollment. Events in randomized subjects from both stages of enrollment will support the final analysis. Additional subjects may be recruited if withdrawal rates during the lead-in period are greater than anticipated. - The study will be conducted at approximately 300 centers.

- The study consists of three periods:
 - 1) **Screening Period** (starting at Visit 1 with informed consent): up to 2 weeks to verify eligibility prior to the first dose of study medication in the lead-in period.
 - 2) **Lead-in Period** (starting at Visit 2): single-blind, 2-week period during which the subjects will receive 8 mg naltrexone SR/90 mg bupropion SR (NB) once a day for the first week and placebo once a day for the second week. The intent of the lead-in period is to identify subjects who do not tolerate treatment with NB well or who exhibit other characteristics that would predict lack of compliance. Subjects who discontinue study medication treatment during the lead-in period will not be randomized or participate in subsequent study procedures.
 - 3) **Treatment Period** (starting at Visit 3): double-blind, randomized period during which the subjects who completed the lead-in period and satisfied inclusion/exclusion criteria will receive NB or placebo. The treatment period starts upon randomization at Visit 3. Randomized treatment assignment will be via an internet- or telephone-accessed centralized computer-based system. Each site will be identified by a unique number, and each subject will have a unique identifier assigned.
 - a) At Visit 6 (Week 16) there will be an assessment of weight loss and blood pressure changes relative to baseline observations. The target weight loss is $\geq 5\%$ with expected minimum weight loss at 16 weeks of $\geq 2\%$. Subjects should be discontinued from study medication at Week 16 if:
 - they have not lost at least 2% of their body weight *or*
 - they are experiencing sustained (b) (4) increases in blood pressure (systolic or diastolic) of ≥ 10 mm Hg (or other increases deemed clinically relevant by the Investigator). If the Investigator suspects that an elevated blood pressure measurement may be spurious, subjects should not be discontinued until the elevated measurement is reconfirmed.
 - b) All subjects will be asked to participate in a weight management program that includes educational resources, weight tracking and goals, meal tracking in combination with a low fat, calorie counting plan, activity tracking, and internet- or telephone-based group counseling meetings as well as access to registered dietitians. Subjects who discontinue study medication prematurely will be encouraged to continue in the weight management program.
 - c) Every other month between visits past Week 26, subjects will be asked to answer specific questions pertaining to compliance and hospitalizations (potential MACE or serious adverse events [SAEs]), using an internet- or telephone-based data collection system.
 - d) All randomized subjects who discontinue study medication early will complete the end-of-treatment visit procedures and continue to be followed for the remainder of the study for collection of MACE data. Subjects will be asked to come to the study site at their scheduled visits and complete the internet- or telephone-based data collection every other month between visits past Week 26 even though they are no longer taking study medication.



STUDY POPULATION

Overweight and obese subjects with cardiovascular risk factors such as diagnosed atherosclerotic vascular disease or type 2 diabetes mellitus requiring pharmacotherapy with at least 2 of 3 additional comorbidities (hypertension, dyslipidemia, or current tobacco smoker) are eligible to participate in this study. Approximately 9,876 subjects will be enrolled into the single-blind lead in, and of those it is anticipated that 9,186 will be randomized into the double-blind treatment period.

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

- ≥ 50 years of age (women) or ≥ 45 years of age (men)
- Body mass index (BMI) $\geq 27 \text{ kg/m}^2$ and $\leq 50 \text{ kg/m}^2$
- Waist circumference $\geq 88 \text{ cm}$ (women) or $\geq 102 \text{ cm}$ (men)
- Have a diagnosis of at least one of the following:
 - Atherosclerotic vascular disease (including coronary disease and peripheral arterial disease, but excluding cerebrovascular disease)
 - Type 2 diabetes mellitus requiring pharmacotherapy with at least 2 of the following 3 comorbidities: (1) hypertension (controlled with pharmacotherapy at $<140/90 \text{ mm Hg}$); (2) dyslipidemia requiring pharmacotherapy; (3) current tobacco smoker.

Exclusion Criteria

- Myocardial infarction within 3 months prior to screening
- Clinical history of cerebrovascular disease (stroke)
- Blood pressure $\geq 140/90 \text{ mm Hg}$, irrespective of treatment with antihypertensive agents
- Unstable weight within 3 months prior to screening (e.g., weight gain or loss of $>3\%$)
- Planned bariatric surgery, cardiac surgery, or coronary angioplasty
- Clinical history of severe renal impairment or documented estimated GFR $<30 \text{ mL/min}$
- Clinical history of liver failure or documented ALT or AST greater than 3 times the upper limit of normal (ULN)
- Known infection with HIV or hepatitis
- Chronic use or positive screen for opioids
- Recent drug or alcohol abuse or dependence (with the exception of nicotine dependence) within 6 months prior to screening
- History of seizures, cranial trauma, or other conditions that predispose the subject to seizures
- History of mania or current diagnosis of active psychosis, active bulimia or anorexia nervosa (binge eating disorder is not exclusionary)
- At risk for suicide attempts based on the judgment of the Investigator

- A clinically meaningful acute exacerbation of depressive illness at screening
- Any condition with life expectancy anticipated to be less than 4 years (e.g., congestive heart failure NYHA Class 3 and 4, active malignancies)
- Current use of other bupropion or naltrexone containing products
- Use of monoamine oxidase inhibitors within 14 days prior to screening
- Use of any investigational drug, device, or procedure within 30 days prior to screening
- History of hypersensitivity or intolerance to naltrexone or bupropion
- Pregnant or breast-feeding women, or currently trying to become pregnant, or of child-bearing potential and not willing to practice birth control
- Employment by the Sponsor or co-habitation with another individual enrolled in the study

STUDY MEDICATIONS

- The study medication (NB and placebo) will be provided as tablets. Each active tablet will contain 8 mg naltrexone SR/90 mg bupropion SR (8/90). All tablets, including placebo, will be identical in appearance to maintain blinding. Dose escalation will occur during the first 4 weeks of the treatment period, as shown in the table below.
- Route of Administration: Oral. Doses can be taken with or without food.

Dose Schedule	Lead-in Period		Treatment Period			
	Week -2	Week -1	Week 1 (Days 1-7)	Week 2 (Days 8-14)	Week 3 (Days 15-21)	Week 4 through end of study
<i>Total Daily Dose*</i>	8/90 NB	--	8/90 NB	16/180 NB	24/270 NB	32/360 NB
Morning	1 tab NB	1 tab PBO	1 tab NB or PBO	1 tab NB or PBO	2 tabs NB or PBO	2 tabs NB or PBO
Evening	--	--	--	1 tab NB or PBO	1 tab NB or PBO	2 tabs NB or PBO

*Doses shown are of naltrexone SR/bupropion SR (NB); tab=tablet; PBO=placebo.

- **Drug Distribution and Reconciliation**
Study medication will be distributed to subjects at site visits. Subject compliance with study medication dosing will be assessed at study visits and every other month through internet- or telephone-based subject questioning between visits after Week 26. Used and partially used bottles will be returned to the site at each designated visit. Reconciliation of distributed versus returned study medication bottles will occur at the study site, and returned study medication will be shipped back to the depot.

STUDY PROCEDURES

See Schedule of Study Procedures (Appendix 2).

ADVERSE EVENT COLLECTION

Potential cardiovascular events occurring during the lead-in and randomized treatment period of the study will be collected and subjected to adjudication by an independent Clinical Endpoint Committee (CEC) to identify those events that meet the MACE endpoint definition. Deaths and potential cardiovascular events specified in this trial as outcome events will be exempted from the usual expedited regulatory reporting requirements, in keeping with 21CFR 312.32(c)(5). All parties involved with the trial are to remain blinded to treatment assignment for subjects that have such events. Consistent with the well established general safety profile from both the NB phase 3 program and extensive clinical experience of both individual NB components, routine safety data collection will be limited to adverse events leading to discontinuation of study medication and SAEs. Information on in utero exposures and pregnancy outcomes will also be collected. Safety data will be reviewed on an ongoing basis by an independent Data Monitoring Committee (DMC).

STATISTICAL ANALYSIS

Primary Endpoint:

- Time from randomization to the first confirmed occurrence of MACE (any of the following events: cardiovascular death, nonfatal myocardial infarction, (b) (4), (b) (4), or nonfatal stroke).

Analysis Populations and Data Considerations:

- **Enrolled:** Subjects who take at least one dose of study medication during the lead-in period. Data from this population will not be used in any formal statistical analyses.
- **Intent-to-treat (ITT):** Subjects who are randomized and dispensed study medication. All post-randomization data will be included in statistical analyses for this population. The ITT population will be the primary analysis population for the primary endpoint and all secondary endpoints.
- **Per Protocol:** ITT subjects who take at least one dose of study medication in accordance with the study protocol. Post-randomization data values observed within 30 days of a subject's last confirmed dose date will be included in all analyses for the Per Protocol population (referred to as on-treatment data), while data values outside of this window will be excluded. The Per Protocol population will be used for sensitivity analyses.

Hypotheses for the Primary Endpoint and Testing Procedure:

With respect to the primary endpoint, the following 3 null hypotheses will be tested:

- H01: The hazard ratio for NB32 relative to placebo is ≥ 2.0
- H02: The hazard ratio for NB32 relative to placebo is ≥ 1.4
- (b) (4)

In order to control the Type 1 error rate at the one-sided $\alpha=0.025$ level, a (b) (4) procedure will be used. The testing procedure is described below and will be based on MACE confirmed by adjudication.

- Accrue 87 events.
- Conduct analysis to rule out a non-inferiority (NI) margin of 2.0 using all of alpha (testing H01).
- The trial must stop if the NI margin of 2.0 is not met. Note that when the true underlying hazard ratio is equal to 1, the least favorable hazard ratio point estimate that will still result in non-inferiority for this test is 1.314.
- If the NI margin of 2.0 is met, all of alpha is recovered; the trial will proceed to 371 events to rule out the NI margin of 1.4 at the end of the study (testing H02).
- The final analysis to rule out the NI margin of 1.4 is conducted using all of alpha without adjustment since it will be the first analysis against the NI margin of 1.4. The first analysis with 87 events will not be used to rule out the NI margin of 1.4 and hence no multiplicity control is needed between this analysis and the analyses against the NI margin of 2.0. Note that when the true underlying hazard ratio is equal to 1, the least favorable hazard ratio point estimate that will still result in non-inferiority for this test is 1.142.
- (b) (4)

Choice of NI Margin:

In a study population with an annual background MACE rate of 1.0-1.5%:

- The pre-approval NI margin of 2.0 corresponds to ruling out an excess of 10-15 additional events per 1000 subject-years with an absolute risk difference of 1.0-1.5%.
- The post-approval NI margin of 1.4 corresponds to ruling out an excess of 4-6 additional events per 1000 subject-years with an absolute risk difference of 0.4-0.6%.

Data Monitoring Committee (DMC):

An independent DMC will be formed prior to study initiation and will have as its primary objective the monitoring of subject safety. The DMC will abide by principles set forth in the FDA Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees, and is described thereafter as per the FDA's definition. The DMC will be composed of individuals external to the study organizers, sponsors, and investigators and will operate under a written charter that includes standard operating procedures. The DMC will

conduct reviews of accumulating data from the study on a regular basis and will advise the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DMC will evaluate relative treatment effects based on protocol-specified endpoints to determine if the trial is meeting its objectives. A statistical approach that permits multiple interim data reviews while maintaining the Type I error rate at the desired level will be pre-specified and will use standard group sequential methodology.

Analysis Methods for the Primary Hypotheses:

As described in the testing procedure for the primary endpoint, two NI analyses are planned. The first analysis will be conducted while the study is ongoing after 87 confirmed MACE are accrued. A second analysis will be conducted after 371 confirmed MACE are accrued and the study is completed. (b) (4)

(b) (4) For each of the primary hypotheses, the ITT population will be used in the primary analysis and an on-treatment analysis using the Per Protocol population will be conducted as a sensitivity analysis. A Cox proportional hazards model will be employed, with treatment, sex and baseline cardiovascular risk group as factors, and age as a covariate. Point estimates and confidence intervals for hazard ratios will be obtained within the framework of this model.

Secondary Endpoints:

- Time from randomization to the confirmed occurrence of cardiovascular death (including fatal myocardial infarction, fatal unstable angina requiring hospitalization, fatal stroke)
- Time from randomization to the first confirmed occurrence of myocardial infarction
- (b) (4)
- Time from randomization to the first confirmed occurrence of stroke (b) (4)
- (b) (4)

Other Endpoints:

- Time from randomization to the confirmed occurrence of death from any cause
- Time from randomization to the first occurrence of coronary revascularization procedure
- Percent change in body weight from baseline to Week 52
- Proportion of subjects achieving $\geq 10\%$ body weight from baseline at Week 52
- Change in blood pressure from baseline to Week 52

Sample Size:

The following assumptions were used to determine the number of confirmed MACE required for the final analysis against a NI margin of 1.4 for the primary hypothesis in the primary analysis population (ITT).

- Underlying hazard ratio of active to control: 1
- NI margin: 1.4
- One-sided $\alpha = 0.025$
- At least 90% power at the final analysis to establish that the upper bound of a one-sided 97.5% confidence interval for the hazard ratio will fall below the pre-specified NI margin.

Under these assumptions, the trial will require 371 events. Similarly, 87 events will provide 90% power for the NI margin of 2.0.

To estimate sample size for the ITT population, the following assumptions are used in addition to those listed above. These assumptions are necessary to allow a sample size to be calculated. However, since this is an event-driven study, the power for the study is based on the number of MACE rather than the number of subjects. The assumptions used below represent a single cohort of subjects randomized in one stage for the final analysis and do not incorporate potential variations such as enrollment of subjects in more than one stage. Accordingly, the actual sample size may vary from the sample size calculation provided in this protocol depending on the actual accrual of events.

- Recruitment period: (b) (4) years
- 1:1 randomization
- Maximum subject follow-up: 4 years
- Lost to follow up (LTFU) rate: 0.012 annual LTFU
- Primary MACE endpoint annualized event rate: 1.5% in the control group

Under these assumptions, the trial will require N=3,955 subjects per treatment group. However, the number of subjects planned is N=4,593 per treatment group to allow for accrual of a sufficient number of events in case of minor departures from event rate, recruitment and retention rates, and underlying hazard ratio assumptions.

This event-driven study will be stopped when 371 MACE have been confirmed. Accrual of 371 confirmed MACE will provide 90% power for the primary analysis with a NI margin of 1.4 in the ITT population (H02). The least favorable hazard ratio that can still result in a non-inferiority result for H02 is 1.142 when the true underlying hazard ratio is equal to 1. With this number of events and the expected discontinuation rate from study medication, it is anticipated that there will be a sufficient number of confirmed on-treatment MACE to provide high probability that the hazard ratio estimate in the Per Protocol population is less than 1.142 assuming the true underlying hazard ratio is equal to 1.

Similarly, in the analysis using a NI margin of 2.0, accrual of 87 confirmed MACE will provide 90% power in the ITT population with the least favorable hazard ratio that can still result in a non-inferiority result for H01 being 1.314 when the true underlying hazard ratio is equal to 1. It is anticipated that there will be a sufficient number of confirmed on-treatment MACE to provide high probability that the hazard ratio estimate in the Per Protocol population is less than 1.314 assuming the true underlying hazard ratio is equal to 1.

APPENDIX 2: SCHEDULE OF STUDY PROCEDURES

	Screening Period	Lead-in Period	Treatment Period							Remote Contacts ⁷
	Visit 1 (Screening)	Visit 2 (Week -2)	Visit 3 (Day 1) (Baseline)	Visit 4 (Week 2)	Visit 5 (Week 8)	Visit 6 (Week 16)	Visit 7-13 (Weeks 26, 52, 78, 104, 130, 156, 182)	Visit 14 (Week 208) (End-of-Study Visit) ⁵	End-of-Treatment Visit ⁶	
Informed Consent	X									
Eligibility Criteria	X	X	X (labs)							
Demographics	X									
Medical History	X									
Height	X									
Weight	X		X	X	X	X	X	X	X	
Waist Circumference	X							X	X	
Vital Signs (BP and HR)	X	X	X	X	X	X	X	X	X	
Electrocardiogram		X								
Pregnancy Test (urine) ¹		X								
Drug Screen (urine)		X								
Concomitant Medications	X							X	X	
Lipids, HbA1c, hsCRP		X								
Chemistry, Hematology, Urinalysis ²		X								
MACE			X	X	X	X	X	X	X	X
Query First Diagnosis T2DM				X	X	X	X	X	X	
SAEs, AEs Leading to Withdrawal, Pregnancies			X	X	X	X	X	X	X	X
Randomization			X							
Study Training		X	X							
Weight Management Counseling ³			→							
Evaluation to Continue Treatment						X				
Study Medication Dispensing/Return ⁴		X	X		X	X	X	X	X	
Drug Compliance			X	X	X	X	X	X	X	X

Post-baseline visit windows are ± 3 days at Visit 4, ± 1 week at Visits 5 and 6, ± 2 weeks for subsequent visits during the first year of the study, and ± 4 weeks for all visits beyond the first year.

¹Women of child-bearing potential only.

²Chemistry (fasting): albumin, AST, ALT, bilirubin (Direct/Indirect), BUN, calcium, creatinine, glucose, phosphorus and uric acid; Hematology: CBC with differential and platelet count; Urinalysis: appearance, specific gravity, pH, dipstick for protein, blood, glucose, ketones, microscopic examination of sediment.

³Frequency of counseling sessions will be as follows: once per week for 16 weeks; once every other week for 8 weeks; monthly through 78 weeks, and two 4-week refreshers during Years 3 and 4.

⁴Visit 2 = dispensing only; Visit 14, End-of-Study Visit, and End-of-Treatment Visit= return only.

⁵Subjects with an end-of-treatment visit will not return study medication or have compliance or concomitant medications recorded at Visit 14/end-of-study

⁶Subjects who discontinue study medication before Week 208 will be asked to return to the study site for the indicated end-of-treatment assessments, and asked to return for their remaining visits through Week 208 for follow-up.

⁷After Visit 7 and through the remainder of the study, subjects will answer specific questions pertaining to compliance and any occurrence of hospitalizations through an internet- or telephone-based data collection system every 2 months between visits. Hospitalization information will be used to identify potential MACE or SAEs.

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

/s/

EILEEN M CRAIG
11/15/2011

ERIC C COLMAN
11/15/2011

9-15-11



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 200063

DISPUTE APPEAL – DENIED

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines, Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone hydrochloride and bupropion hydrochloride extended-release tablets).

We also refer to your July 14, 2011, request for formal dispute resolution, received on July 14, 2011, to the Office of New Drugs. The request for dispute resolution concerns the requirement, stated in our January 31, 2011, complete response (CR) letter, for a pre-approval randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with Contrave does not adversely affect the drug's benefit-risk profile. This formal dispute request follows your June 8, 2011, appeal to the Office of Drug Evaluation II (ODEII) and subsequent denial of your appeal on July 7, 2011, by Dr. Curtis Rosebraugh, Director, ODEII.

I have carefully reviewed the materials you submitted in support of your appeal, the reviews and decision memoranda prepared by FDA staff, the CR letter, Dr. Rosebraugh's appeal denied letter, and other pertinent material (e.g., materials and transcript from the December 7, 2010, Endocrinologic and Metabolic Drugs Advisory Committee meeting). I have also consulted with staff in ODEII, the Office of Biostatistics, the Office of Surveillance and Epidemiology, Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products, and Dr. Robert Temple, Deputy Center Director for Clinical Science.

I have completed my review of your request for formal dispute resolution and deny your appeal. I agree with the Division of Metabolism and Endocrinology Products (DMEP) and ODEII that additional data are needed regarding the cardiovascular (CV) safety of Contrave prior to approval to inform our benefit risk evaluation. I believe there is a path forward for how you can collect the necessary data in an efficient and timely manner so as not to unnecessarily delay approval if you are able to demonstrate that Contrave does not unacceptably increase the risk of major adverse cardiovascular events (MACE) in overweight and obese patients. I will provide comments on this path forward after I address your specific questions.

Dr. Rosebraugh's appeal denied letter provided an excellent summary of the relevant data that informed our decision, so I will not repeat a detailed description of the data here. I will focus instead on the overarching safety and policy issues that underlie our decision.

The primary issue in dispute is whether additional safety data are required prior to approval to evaluate the adverse cardiovascular impact, if any, of chronic use of Contrave in overweight and obese patients. This concern is derived from the fact that in controlled clinical trials Contrave caused a sustained, albeit modest, higher mean blood pressure compared to patients treated with placebo, even though Contrave was associated with greater weight loss than placebo. Based on this finding, DMEP and ODEII concluded that additional CV safety data are required to inform the Agency's benefit risk evaluation of Contrave prior to approval. I concur with that decision.

Our decision is based on the data contained in the Contrave NDA along with the Agency's experience with other sympathomimetic drugs and dietary supplements for treatment of obesity. As you know, two obesity drugs and one dietary supplement (i.e., phenylpropanolamine [PPA], sibutramine, and ephedra) that were associated with adverse blood pressure effects were shown to increase the risk of serious, and sometimes fatal, cardiovascular events (such as stroke and myocardial infarction) and have been removed from the U.S. market by FDA. While there are many reasons for pharmacologic treatment of obesity, one of the main goals is to reduce an individual patient's risk of cardiovascular disease. The sibutramine case, in particular, has taught us that even modest drug-induced effects on mean blood pressure, either as a direct effect or acting indirectly through some other mechanism such as increased sympathetic tone, in obese patients can offset any positive cardiovascular benefit of drug-induced weight loss and lead to a paradoxical increase in cardiovascular risk. Our decision on the benefit risk of Contrave must be informed by all available data and prior Agency actions.

While there are some differences in the available data on the effect of Contrave and sibutramine on weight loss and cardiovascular risk factors, there are no head-to-head controlled clinical trials to support your claims, based on cross-study comparisons of sometimes different trial designs, populations, and duration, that Contrave has a better effect on CV risk factors than sibutramine or that these hypothesized differences will translate to a different CV risk profile. Further, as Dr. Rosebraugh noted, history has taught us that drug-induced changes in CV risk factors, such as increasing HDL and decreasing HbA1c, do not always translate into the expected CV benefit when tested in controlled clinical trials.

In the absence of additional CV safety data, I do not share your confidence that we can conclude that Contrave has a different (i.e., lesser or no) effect on CV safety than sibutramine. Despite your assertions to the contrary, I find the overall theme from the available data for the two drugs to be quite similar. In controlled clinical trials both drugs caused sustained higher mean blood pressure compared to placebo in overweight and obese patients, even in the face of greater weight loss in the drug treatment groups. For example, in the ambulatory blood pressure sub-study, after 52 weeks of treatment with Contrave or placebo, the blood pressure effect of Contrave was still evident in drug-treated patients. This effect was seen despite the fact that Contrave-treated patients experienced a significantly greater weight loss compared to placebo-treated patients, which would have been expected to have resulted in significantly lower blood pressure. In fact, the mean 24-hour blood pressure in Contrave-treated patients at week 52 was essentially the same as their baseline despite an average weight loss of 7.5%. This sustained higher blood pressure over placebo is of significant concern given what we know from epidemiologic data regarding the adverse CV effects of elevated

blood pressure, the high prevalence of hypertension in obese patients, and the results of the CV outcomes trial (SCOUT) conducted with sibutramine.

In the case of sibutramine, the SCOUT trial demonstrated a significantly increased risk of MACE in patients treated with sibutramine. These data led the Agency to conclude that the benefits of the drug did not outweigh its risks in the treatment of obesity, and resulted in market withdrawal of sibutramine in October, 2010. While it is true that Contrave “is not sibutramine,” as you remind us in your appeal, it would be inappropriate for us to ignore the lessons learned from sibutramine as we evaluate the benefits and risks of Contrave where we see a very similar blood pressure signal.

As noted by Dr. Rosebraugh, there were very few MACE events in the controlled trials for Contrave. This is not surprising since the trials were conducted in a generally low CV risk patient population. The available data are not adequate to provide assurance that chronic use of Contrave is not associated with an unacceptable increase in CV risk that would offset its modest mean effect on weight loss. Prior to approval it is critical that we have adequate data to assess the CV risk of Contrave so that an informed benefit risk analysis can be performed. Such data are needed not only to inform the approval decision, but also to judge whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of Contrave outweigh its risks if approval is granted.

In your initial response to the CR letter in preparation for the end-of-review meeting, you proposed to conduct the requested CV outcomes trial prior to approval. Your proposed trial included assessment of a risk mitigation strategy for the blood pressure effect (e.g., careful monitoring of patients for blood pressure increases, discontinuation of treatment after a defined time period if a sufficient amount of weight loss had not occurred) and you proposed to conduct an interim analysis that might support approval before completion of the trial if the data met pre-specified criteria for exclusion of CV risk of a certain magnitude. The interim analysis approach is similar to the strategy the Agency has implemented with regard to CV risk assessment for drugs to treat diabetes mellitus. DMEP and ODEII were willing to consider this proposal, however, agreement was not reached on a trial that we considered interpretable and informative and that you considered feasible to conduct in a timely manner.

You subsequently changed your approach and are now proposing that Contrave be approved initially for a low CV risk population of patients under a REMS with Elements to Assure Safe Use (ETASU), including restricted distribution, and that the CV outcomes trial be completed after approval. I do not find the new approach to be a reasonable path forward to address the safety concerns associated with Contrave.

As I noted earlier, we currently do not have enough data to inform the benefit risk assessment for Contrave to support approval. A REMS with ETASU is not a substitute for collecting the data needed to define the risk in question, particularly given the recent withdrawal of sibutramine and the fact that the necessary data can be obtained from a CV outcomes trial that is feasible and can be completed in a reasonable time frame. We need additional data to inform an adequate assessment of whether the benefits of Contrave outweigh its risks, and if that assessment were to support approval we would then consider the need for a REMS to ensure safe use.

I do not find your suggested limited patient population to be a logical one in which to implement a highly restrictive REMS with ETASU, including restricted distribution, as you have proposed. The limitation of use to patients without co-morbid conditions, such as diabetes and CV disease, excludes

those obese patients in whom there is arguably the greatest need for new safe and effective obesity treatments. Such a population is also at odds with how the Agency has approached the use of REMS with ETASU, which have generally been reserved for patients with more severe, advanced disease where the impact of the disease makes additional risk and additional burdens on the healthcare system acceptable. It appears that you have targeted a low CV risk population with the expectation that the weight loss benefit of the drug will outweigh the risks, if any, associated with the blood pressure effect, however there are no data to support a positive benefit risk in this population and there are no data to support your conclusion that the REMS procedures will actually mitigate any excess CV risk.

During our meeting on August 16, 2011, we discussed your rationale for selecting a low CV risk population for limited marketing and also discussed why you were not proposing to limit use to higher CV risk obese patients. While on its face, it may seem more logical to restrict use to a higher CV risk population with co-morbidities such as diabetes and CV disease, this is also the population in which there would be the greatest concern about the impact of the blood pressure effect of Contrave on CV risk. Given the experience with SCOUT, which was conducted in a higher risk patient population, I agree with your conclusion that additional data are required to evaluate the CV risk of Contrave before it could be approved for use in this patient population.

I am aware that there was frustration on both sides relating to discussions of the proposed CV outcomes trial and the inability to reach agreement on an informative and feasible trial. I have worked with the review team in DMEP and ODEII to reconsider our recommendations for the trial and acceptable analytic parameters. We believe that our new proposals would allow for a trial that is feasible and will provide interim results to support consideration for approval in a reasonable time frame. I will outline the details of our proposed CV outcomes trial and analysis criteria at the end of this letter after I respond to the five specific questions you raised in your appeal (repeated below in bold italics followed by my response).

Whether the Data in the CONTRAVE NDA Provide Sufficient Information Regarding the Benefit-Risk Profile on Contrave to Permit Approval with Appropriate Labeling, Risk Management, and Post Approval Commitments

As noted by Dr. Rosebraugh, the data for Contrave met one of the two efficacy criteria established by the Agency in our 2007 draft Guidance to Industry: Developing Products for Weight Management¹. So, while Contrave has passed the “floor” criteria for demonstrating efficacy in weight loss we also consider the magnitude of demonstrated benefit in our benefit risk assessment. While a showing that Contrave has met at least one of the criteria for efficacy stated in the Guidance is necessary to support approval, such a showing is not necessarily sufficient to result in a positive benefit risk assessment for approval if a significant safety concern is noted, such as the blood pressure effect seen with Contrave and its potential impact on MACE. As I noted earlier, the available data to assess the impact of the blood pressure effect of Contrave on MACE are inadequate to inform our benefit risk assessment for approval. More data are needed to provide assurance that Contrave does not paradoxically increase the risk of MACE even in the face of greater weight loss than placebo. These data are necessary to support an approval decision and inform any necessary labeling, REMS, and post-approval requirements/commitments. It is not appropriate to substitute a REMS for an adequate assessment of the safety of the product for the proposed use.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf>

Whether the DATA in the CONTRAVE NDA Demonstrate a Favorable Benefit-Risk Profile of Contrave in Patients Without Type 2 Diabetes, Active CV Disease, or Non-Responders, so as to Permit Approval for this Limited Population with Appropriate Labeling, Risk Management, and Post-Approval Commitments

As noted above, the available data to evaluate the impact of the blood pressure effect of Contrave on the CV risk are inadequate to support a benefit risk assessment in any patient population. While it is true that the absolute risk for CV disease is low in the population of patients you have selected for proposed limited approval, we have inadequate data to inform a conclusion that the benefits of the drug outweigh its risks in this patient population or that the proposed risk management procedures will actually mitigate any CV risk associated with Contrave. Additional data on CV outcomes in patients treated with Contrave are needed to inform our benefit risk decision for the population of overweight and obese patients as a whole and for particular subgroups of patients. As stated previously, it is not appropriate to substitute a REMS for an evaluation of the risks, particularly given the history of safety concerns with drugs to treat obesity that exhibited an adverse effect on blood pressure and the fact that answers to these questions can be obtained from a controlled clinical trials in a reasonable timeframe.

Whether the Requirement for a Pre-Approval Cardiovascular Outcomes Study for CONTRAVE is Consistent with Recent FDA Actions on Similarly Situated Products

A definition of “similarly situated products” is subject to individual interpretation. Dr. Rosebraugh addressed the non-obesity examples you cited, however, I believe the most appropriate “similarly situated products” to Contrave on which to make comparisons are other drugs proposed for/approved for the treatment of obesity, such as rimonabant, phentermine/topiramate, lorcaserin, and sibutramine. I believe that FDA has treated Contrave similarly to how are have treated other drugs for obesity.

Three of these four products have not been approved by FDA despite the fact that each NDA included data to show that the drug had met the at least one of the efficacy criteria specified in the 2007 draft guidance. In each case for the drugs that have not been approved, including Contrave, the Agency identified significant safety concerns that needed to be further evaluated prior to approval in order to inform our benefit risk assessment. In each case we advised the sponsor on the types of safety data that were needed to support approval and this advice was tailored to address the specific concern applicable to each product.

As I noted earlier, our decision on the Contrave NDA is informed by our experience with sibutramine. You suggest in your appeal that we are not treating Contrave fairly since we did not require a pre-approval cardiovascular outcomes trial for sibutramine despite the fact that we were aware at the time of approval of the effect of sibutramine on blood pressure. The implication is that we should ignore the sibutramine experience and follow the same path with Contrave; i.e., require an adequate assessment of the effect on blood pressure after approval, and presumably, withdraw the drug if the outcome trial provides data similar to that seen with sibutramine. I do not find this to be a responsible path forward. As a public health agency we must learn from advances in science and newly available data and apply that new information to current and future decisions. There are numerous examples of cases where new data have informed our regulatory requirements (e.g., our understanding of drug-induced effects on QT prolongation, concerns about the CV safety of drugs for diabetes) going forward. In those cases, the new requirements have been applied to products under development, even though it may not have felt “fair” to the sponsors of those products.

As noted by Dr. Rosebraugh, you were alerted by DMEP in 2007 that the results of SCOUT may have an impact on your development program. In your appeal you now assert that a “reasonable” sponsor would conclude that this advice would translate to a post-approval requirement for a cardiovascular outcomes trial, presumably regardless of the SCOUT outcome. This interpretation of the Agency’s advice, in the face of the results of SCOUT, which showed a statistically significant adverse effect on MACE, and the Agency’s request that Abbott voluntarily withdraw sibutramine from the U.S. market in October 2010, is not reasonable.

In summary, we have treated Contrave fairly and consistent with how we have treated other recent obesity drug applications for approval. We have also appropriately considered our experience with obesity drugs that have been withdrawn from the U.S. market, including the similarly situated drug sibutramine, in our decision making.

Whether the Proposed Labeling and REMS can Adequately Mitigate any Potential Cardiovascular Outcomes Risk and Thereby Alter the Risk-Benefit Profile in a Manner Sufficient for Approval

As I have noted earlier, the available data are inadequate to allow an assessment of the cardiovascular risk of Contrave and such data are necessary prior to approval to inform our benefit risk assessment. The proposed REMS is designed to mitigate the risk for adverse CV outcomes from Contrave by limiting the eligible patient population, carefully monitoring for increases in blood pressure, and stopping drug after a specified period if an individual patient has not lost a specified amount of weight. This paradigm is the same as what you have proposed to study in your cardiovascular outcomes trial. I believe it is prudent to require additional data prior to approval to better assess the CV risk of Contrave and the ability of the proposed REMS to mitigate those risks, if present. While some of your proposals seem logical (i.e., stopping the drug in non-responders), we do not have adequate data to assess the CV risks to obese patients initiated/maintained on Contrave. Given the similarities between Contrave and sibutramine, it is prudent to collect additional CV safety data before approval to better inform our benefit risk assessment.

Whether the Efficacy Thresholds Set Forth in the Weight Loss Guidance are Consistent with FDA’s Current View of Demonstrating Benefit in an Overweight or Obese Population Without Other Co-morbidities

The 2007 draft guidance continues to reflect the Agency’s views on the minimum thresholds for demonstration of efficacy for a weight loss drug. As I noted earlier, meeting at least one of the thresholds is necessary, but not always sufficient, to support a positive benefit risk assessment for a weight loss drug. The benefits for a drug must always be weighed against its risks. In assessing benefits and risks we do not simply look at a categorical “yes/no” of whether the thresholds for efficacy have been met, we also consider the magnitude of the demonstrated effect and weigh that against the seriousness of the drug’s risks, including potential risks that have not yet been adequately characterized. In the case of Contrave, we have concluded that the available data do not support a conclusion that the benefits outweigh the risks and believe that additional data on the cardiovascular safety of the drug are required prior to approval.

Since your end-of-review meeting with DMEP in May 2011, we have continued to consider the design and analysis of the required pre-approval cardiovascular outcomes trial for Contrave. We are now able to provide specific advice on the trial that would support our assessment for approval, and this advice should provide you with the certainty you need to proceed with the trial. While we still plan to

convene a public advisory committee meeting to discuss topics related to obesity drug development early next year, that meeting will not impact on the advice provided in this letter and the Agency will honor the advice provided.

I will outline the broad trial design and analysis parameters here, and I strongly encourage you to schedule a meeting with DMEP to discuss the specific details of your protocol once it is more fully developed. I will be happy to attend that meeting if my schedule permits. I also strongly encourage you to take advantage of the Special Protocol Assessment (SPA)² procedures for this trial.

The trial should enroll a population of overweight and obese patients with an estimated background annual risk of MACE of 1.0-1.5%. There should be a reasonable representation of patients at higher risk, such as patients who have a history of cardiovascular disease. Enrollment of a population with this level of background risk will accomplish two important goals. First, it will help to limit the study sample size and allow for a trial that is feasible to conduct in a reasonable time frame. Second, it will provide information about the safety of Contrave across the spectrum of obese patients who are likely to seek pharmacotherapy. The trial should follow patients long enough to allow an assessment of the long-term safety; i.e., 2-3 years. We do not object to your proposal to stop drug therapy in patients who are not experiencing some pre-specified level of weight loss, but all patients should continue to be followed once off study drug for CV events.

With regard to the criteria for the interim and final analyses, we agree that the intent-to-treat analysis will be considered primary. We will also look at the per-protocol analysis, but the trial does not need to be powered based on that analysis. We believe the criteria for interpretation of the trial should be similar to those that are applied to diabetes drugs; albeit with some differences to account for the expected lower background risk of CV events. For a population with a background risk of 1.0-1.5%, this would translate to a final analysis that excludes a hazard ratio of 1.4 (upper bound of the 95% CI). The interim analysis should exclude a hazard ratio of 2.0 (upper bound of the 95% CI). In both cases, we are no longer requiring specific power calculations based on the observed point estimate; however, as stated in the diabetes guidance, we will consider the point estimate as part of our review of the data. Based on calculations performed by our statisticians, the final analysis will require approximately 371 events and the interim analysis will require approximately 87 events when powering the study with 90% power and under the parameter assumption that the hazard ratio is 1.0. The attached table provides more detail on the sample size calculation and underlying assumptions. We believe that a trial that meets these criteria is feasible to conduct in a reasonable time frame and will provide data adequate to assess the CV risk of Contrave. If the interim analysis meets the specified criteria to exclude an unacceptable increased CV risk, the drug could be approved (barring any unexpected new safety signals), most likely with a REMS, while the trial is completed.

In summary, I concur with DMEP and ODEII that the available data are not adequate to inform a benefit risk assessment of Contrave for approval and that data from a CV outcomes trial are necessary prior to approval. I have considered your alternative proposal for approval with a REMS with ETASU and a post approval CV outcomes trial and do not find that proposal acceptable. I have worked with the review team to rethink our requirements for the CV outcomes trial and I believe the new expectations achieve our goal of interpretable data and can be obtained in a timely manner.

² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf>

Questions regarding next steps in developing the protocol for the required CV outcomes trial to support your complete response to the CR letter should be directed to Meghna Jairath, Pharm. D., Regulatory Health Project Manager in DMEP, 301-796-4267.

If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

John Jenkins, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

The following table provides sample size calculations using 90% power under the assumption that the true hazard ratio is 1.

Event Rate (per 100 subject years)	Relative Risk									
	1.4	1.5	1.6	1.8	1.9	2.0	2.2	3.0	3.4	

0.5	RD	0.20%	0.25%	0.30%	0.40%	0.45%	0.50%	0.60%	1.00%	1.20%
	EE	2.0	2.5	3.0	4.0	4.5	5.0	6.0	10.0	12.0
	Events	371	255	190	121	102	87	67	34	28
	PY	74200	51000	38000	24200	20400	17400	13400	6800	5600
	PE	1.14	1.17	1.20	1.26	1.29	1.32	1.37	1.54	1.62

1.0	RD	0.4%	0.5%	0.6%	0.8%	0.9%	1.0%	1.2%	2.0%	2.4%
	EE	4.0	5.0	6.0	8.0	9.0	10	12.0	20.0	24.0
	Events	371	255	190	121	102	87	67	34	28
	PY	37100	25500	19000	12100	10200	8700	6700	3400	2800
	PE	1.14	1.17	1.20	1.26	1.29	1.32	1.37	1.54	1.62

1.5	RD	0.6%	0.75%	0.9%	1.2%	1.35%	1.5%	1.8%	3.0%	3.6%
	EE	6.0	7.5	9.0	12.0	13.5	15	18.0	30.0	36.0
	Events	371	255	190	121	102	87	67	34	28
	PY	24733	17000	12666	8066	6800	5800	4466	2266	1866
	PE	1.14	1.17	1.20	1.26	1.29	1.32	1.37	1.54	1.62

RD = Risk Difference (Rate Contrave minus Rate Control)

EE = Excess Events (Events Contrave minus Events Control)

Events = Number of events required for 90% power

PY = Patient years need to observe required events

PE = Maximum value of point estimate for RR in order to meet upper bound threshold.

Note

- Sample size calculations (i.e. number of events needed) are based upon an ITT analysis population

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

/s/

JOHN K JENKINS
09/15/2011

8-31-11



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 200063

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines, Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.

We also refer to the meeting between representatives of your firm and the FDA on August 16, 2011. The purpose of the meeting was to discuss the issues raised in your request for formal dispute resolution dated July 14, 2011.

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) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Senior Regulatory Health Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 16, 2011
TIME: 9:30 am – 11:00 am, EST
LOCATION: White Oak Campus, Building 21, Room 1537
APPLICATION: NDA 200063
DRUG NAME: Naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.
TYPE OF MEETING: Formal Dispute Resolution
MEETING CHAIR: John Jenkins, M.D.
MEETING RECORDER: Amy Bertha

FDA ATTENDEES:

John Jenkins, M.D.	Director, Office of New Drugs
Amy Bertha	Senior Regulatory Health Project Manager, Office of New Drugs
Robert Temple, M.D.	Deputy Director for Clinical Science, Center for Drug Evaluation and Research
Curtis Rosebraugh, M.D. (via telephone)	Director, Office of Drug Evaluation II
Leah Ripper	Associate Director for Regulatory Affairs, Office of Drug Evaluation II
Mark Parks, M.D.	Division Director, Division of Metabolism and Endocrinology Products
Eric Colman, M.D.	Deputy Division Director, Division of Metabolism and Endocrinology Products
Eileen Craig, M.D.	Medical Officer, Division of Metabolism and Endocrinology Products
Meghna Jairath, Pharm.D.	Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products
Pat Madara	Senior Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products
Norman Stockbridge, M.D.	Division Director, Division of Cardiovascular and Renal Products
Aloka Chakravarty, Ph.D.	Division Director, Division of Biometrics VII, Office of Biostatistics
Mat Soukup, Ph.D.	Biometrics Team Leader, Division of Biometrics VII, Office of Biostatistics
Xiao Ding, Ph.D.	Biometrics Reviewer, Division of Biometrics VII, Office of Biostatistics

EXTERNAL CONSTITUENT ATTENDEES:

Preston Klassen, MD, MHS	Head of Global Contrave Program & Sr. Vice President of Product Development, Orexigen Therapeutics, Inc.
Michael Narachi, MA, MBA	President and Chief Executive Officer, Orexigen Therapeutics, Inc.
Kristin Taylor, PhD	Sr. Director, Clinical Development, Orexigen Therapeutics, Inc.
Dawn Viveash, MD	Sr. Vice President, Regulatory Affairs, Orexigen Therapeutics, Inc.
Teri Johnson	Director, Regulatory Affairs, Orexigen Therapeutics, Inc.
Heather Turner, Esq.,	General Counsel & Secretary, Orexigen Therapeutics, Inc.
Josephine Torrente, JD, MS,	Outside regulatory consultant and counsel, Hyman Phelps & McNamara, P.C.
Lawrence Roebel, PhD,	Sr. Director, Regulatory Affairs, Takeda Global Research & Development Center, Inc

BACKGROUND:

Orexigen submitted a formal dispute resolution request to the Office of Drug Evaluation II (ODE II) on June 8, 2011, concerning the complete response action taken on January 31, 2011, specifically the pre-approval requirement for a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. Dr. Curtis Rosebraugh, Director, ODE II denied the appeal on July 7, 2011. Orexigen submitted a formal dispute resolution request to the Office of New Drugs on July 14, 2011. Dr. John Jenkins, Director of the Office of New Drugs is the deciding authority. In the appeal Orexigen requested a meeting with FDA.

MEETING OBJECTIVES:

The objective of this meeting was to discuss the issues surrounding the appeal.

DISCUSSION:

Orexigen presented a couple of slides to open the meeting, and then FDA and Orexigen discussed the issues surrounding the appeal, specifically the following areas:

- The feasibility of conducting a cardiovascular (CV) outcomes trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. High level concepts of the study design (i.e., patient population, size, power) and the timing of the study (pre-approval versus post-approval) were also discussed.
- The proposed indicated patient population. (i.e., why Orexigen is proposing that the drug be used in a low risk group prior to performing a CV outcomes trial, the viewpoints of patient advocacy groups and stakeholders).
- High level concepts around the Risk Evaluation and Mitigation Strategies with Elements to Assure Safe Use (REMS with ETASU) proposed by Orexigen in the Formal Dispute Resolution Request submitted on June 8, 2011 to ODE II. While the proposed REMS with ETASU has not been reviewed by the Division of Metabolism and Endocrinology Products (DMEP), high level concepts were discussed, as this strategy is part of Orexigen's proposed path-forward.
- How should naltrexone/bupropion, a weight loss drug with a pressor effect, be treated in light of the safety concerns with sibutramine, a weight loss drug that was removed from the market due to the drug's pressor effect.

DECISIONS (AGREEMENTS) REACHED:

This meeting was not conducted with the expectation that decisions would be made or agreements reached at the meeting. The issues discussed will be taken into consideration when reaching a decision regarding the formal dispute resolution request which will be made in 30 days from the meeting date.

ATTACHMENTS/HANDOUTS:

Slides from Orexigen presentation.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AMY E BERTHA
08/31/2011

8-16-11

**MEDICAL OFFICER REVIEW OF THE FORMAL DISPUTE RESOLUTION
REQUEST**

NDA: 200063

Supporting Doc. No.: 29; eCTD# 0028

Drug Name: Contrave® (naltrexone HCl and bupropion HCl) Extended-Release Tablets

Sponsor: Orexigen Therapeutics

Proposed Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss, used in conjunction with lifestyle modification. CONTRAVE is proposed for patients with an initial body mass index ≥ 30 kg/m² or ≥ 27 kg/m² with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension)

Date of Submission: 7/14/2011

Reviewing Division: Division of Metabolism and Endocrinology Products

Medical Reviewer: Eileen Craig, MD

Medical Team Leader: Eric Colman, MD

Review Date: 8/16/2011

MO comments on Orexigen's 7-14-2011 FDRR:

Comment #1 (page 2 of 7-14-2011 document): No, ODE II's response states that SCOUT and the subsequent withdrawal of sibutramine from the US market influenced and informed our regulatory decision with CONTRAVE (bupropion/naltrexone). In this reviewer's opinion, the negative results of the SCOUT trial and the subsequent withdrawal of sibutramine from the US market changed the requirement for CV outcomes data for CONTRAVE from a post-approval requirement to a requirement for interim (or pre-approval) data from an appropriately designed CV outcomes trial. This trial is necessary to ensure that Contrave-induced weight loss translates either into a quantifiable CV benefit, or, at a minimum, an acceptable degree of CV risk.

Thus, while SCOUT and the decision to request withdrawal of sibutramine from the market certainly played a role in the regulatory decisions with Contrave, it is important to note that ultimately the Division based the Approval Deficiency on the CONTRAVE data itself. The Contrave data met the minimal categorical weight-loss efficacy criterion yet

was coupled with the expected sympathomimetic agent side-effects of blood pressure/pulse increase and insufficient cardiovascular data.

In addition, there was concern about the safety of bupropion used for smoking cessation that was evaluated in hospitalized smokers with acute cardiovascular disease.¹ A randomized, double-blind placebo-controlled trial assessed the safety and efficacy of 12 weeks of sustained-release bupropion (300 mg) or placebo in 248 smokers admitted for acute cardiovascular disease, primarily myocardial infarction and unstable angina. There were 32 events out of 124 (26%) in the active treatment arm; 22 out of 124 (18%) in the placebo arm. The incidence rate ratio at one year was 1.56 with a confidence interval of .91 to 2.69—consistent with a 269 percent increase in risk. In this trial, bupropion was administered for 12 weeks, the IRR for CV events at Week 12 was 1.22 (CI= 0.64, 2.33). While almost none of the safety outcome measures reached statistical significance, the incidence rate ratio for cardiovascular events at different time points all trended in the direction of harm for the drug. Furthermore, a post-hoc analysis done to explore the nonsignificant difference in cardiovascular events between 3 and 12 months found statistically significantly more cardiovascular events in the bupropion group when over 30 days had elapsed since the patient had taken the drug. Bupropion was used for only 12 weeks in this study and therefore provided limited insight into long-term use in a trial designed to assess CV outcomes.

Table 1: Safety Outcomes in the Trial: Bupropion for Smokers Hospitalized with Acute Cardiovascular Disease

Outcome Measure	Bupropion N=124 N (%)	Placebo N=124 N (%)	Incidence Rate Ratio (95% CI)*
Mortality			
All cause	0 (0%)	2 (2%)	—
Cardiovascular†	0 (0%)	1 (1%)	—
Cardiovascular events‡			
<i>Intention to treat analysis</i>			
Up to 3 months	20 (16%)	17 (14%)	1.22 (0.64-2.33)
Between 3 and 12 months	12 (10%)	5 (4%)	2.58 (0.91-7.32)
Cumulative to 12 months	32 (26%)	22 (18%)	1.56 (0.91-2.69)
<i>Analysis by study drug use§</i>	N=122§	N=122§	
On study drug	15 (12%)	13 (11%)	
≤ 30 days after stopping drug	1 (1%)	4 (3%)	
Total (up to 30 days off drug)	16 (13%)	17 (14%)	1.02 (0.51-2.01)
>30 days after stopping drug	15 (12%)	4 (3%)	3.93 (1.30-11.80)¶
Cumulative to 12 months	31 (25%)	21 (17%)	1.56 (0.90-2.72)
New blood pressure elevation**			
Up to 3 months	16 (13%)	12 (10%)	1.31 (0.62-2.77)
Cumulative to 12 months	16 (13%)	12 (10%)	1.34 (0.64-2.83)
Non-cardiac serious adverse events††			
Up to 3 months	25 (20%)	24 (19%)	1.02 (0.58-1.79)
Cumulative to 12 month	46 (37%)	38 (31%)	1.17 (0.76-1.80)

*Rate of events per person-year of follow-up.

†Cardiovascular death is a death resulting directly from a myocardial infarction, congestive heart failure, cardiac arrhythmia, stroke, any cardiac procedure, or a sudden death. All other deaths were considered to be noncardiovascular deaths.

‡Cardiovascular event is a cardiovascular death, nonfatal MI, hospitalization for unstable angina or congestive heart failure, stroke, or coronary revascularization (angioplasty, stent placement, or coronary

¹ Rigotti NA, Thorndike AN, Regan S, McKool K, Pasternak RC, Chang Y, et al. Bupropion for smokers hospitalized with acute cardiovascular disease. *Am J Med.* 2006 Dec; 119(12):1080- 1087.

bypass surgery). This also represents all patients with cardiac serious adverse events. The number is the number of patients with 1 or more CV event.

§This post-hoc exploratory analysis excludes 4 subjects, 2 in each group, who never took study drug. Two of the 4 excluded subjects had a cardiovascular event, 1 in each group. Hence, total number of events is reduced by 2 in this analysis.

¶ $P < .005$. After adjusting for cardiac risk factors (hyperlipidemia, hypertension, diabetes), history of CHD, discharge diagnosis, and smoking status at the time of the event, IRR is 3.12 (95% CI 1.01-9.65, $P = .05$).

**Number of patients with a first systolic BP > 160 or diastolic BP > 100 recorded at a follow-up visit or by the patient using ambulatory blood pressure monitor during the first 2 weeks after discharge.

††Number of all noncardiac serious adverse events, not just first events in each subject. Results do not differ if the analysis is done based on first events only.

Source: Rigotti NA, Thorndike AN, Regan S, McKool K, Pasternak RC, Chang Y, et al. Bupropion for smokers hospitalized with acute cardiovascular disease. *Am J Med.* 2006 Dec; 119(12):1085.

In conclusion, Contrave did not yield the weight-loss efficacy margin that allowed an acceptable safety trade-off consideration, especially given the adverse blood pressure and heart rate signals.

Comment #2 (page 2 of 7-14-2011 document): “ODE II’s response however, fails to address in sufficient detail the nearly seven pages of data in the FDRR that demonstrate greater efficacy of CONTRAVE over sibutramine in the target patient population, lower hypertensive effects of CONTRAVE relative to sibutramine, sibutramine’s other negative cardiometabolic effects demonstrated in SCOUT that do not occur with CONTRAVE, and the lack of any correlation between blood pressure effects and CV outcomes in SCOUT.”

First off, you cannot fairly compare head-to-head the efficacy and safety data from SCOUT, which enrolled a much sicker population and had a trial duration of ~ 3 ½ years, with the pre-approval clinical trial data from the Contrave submission. However, the Contrave and sibutramine populations evaluated in the pre-approval trials are similar.

We see the efficacy of Contrave as similar to that of sibutramine when comparing the similar populations from the pre-approval Contrave and pre-approval sibutramine database. Again, one cannot compare the efficacy of the SCOUT trial to that of the Contrave pre-approval database—they are very different patient populations and the trial design and duration are disparate. One must compare the pre-approval database for both. One could also comment that Contrave achieved the similar weight-loss efficacy using 2 drugs in combination while other weight loss products such as sibutramine and rimonabant only required one drug to achieve similar efficacy.

Table 2. Mean Weight Change at One Year for Various Obesity Drugs

	Active mean weight change at 1 year	Placebo mean weight change at 1 year	Data Source
Orlistat 120 mg TID	-6.1 kg	-2.6 kg	Xenical prescribing information
Sibutramine 15 mg QD	-6.4 kg	-1.6 kg	Meridia prescribing information
Qnexa (phentermine/topiramate) 15/92 mg QD	-11.4 kg	-1.9 kg	NDA 22580, FDA Briefing Package, EMDAC meeting, 15 July 2010
Lorcaserin 10 mg BID	-5.8 kg	-2.5 kg	NDA 22529, ISE Table 13

NB32 (naltrexone 32 mg /bupropion 360 mg) QD NB-301 (No DM)	-6.1 kg	-1.4kg	Greenway FL, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. www.thelancet.com Published online 30 July 2010.

Table 3: LS Mean Percent Weight Loss at One Year for Various Obesity Drugs Studied for Long-Term Use

	Active LS Mean Percent Weight Loss from Baseline	Placebo LS Mean Percent Weight Loss from Baseline	Treatment Comparison, LS Mean Difference from Placebo	Data Source
Orlistat 120 mg TID Study NM14161	-4.1	-0.3	-3.8	NDA 21887, pg 324/1014
Rimonabant 20 mg QD RIO-North American	-6.5	-1.7	-4.7	NDA 21888, statistical review
RIO-Europe	-6.9	-2.1	-4.7	
RIO-Lipids	-7.4	-1.9	-5.4	
RIO-Diabetes	-5.5	-1.6	-3.9	
Qnexa (phentermine/ topiramate) 15/92 mg QD OB-302 (No DM)	-10.9	-1.6	-9.4	NDA 22580, FDA Briefing Package, EMDAC meeting, 15 July 2010; NDA 22580 CSR OB-302 Table S1 and CSR OB-303 Table S1
OB-303 (16% DM)	-9.8	-1.2	-8.6	
Lorcaserin 10 mg BID APD356-009 BLOOM	-5.9	-2.2	-3.7	NDA 22529, Summary of Clinical Efficacy, Table 12
APD356-011 BLOSSOM (pooled) (No DM)	-5.8	-2.8	-3.0	
	-5.8	-2.5	-3.3	NDA 22529, ISE Table 13
NB32 (naltrexone 32 mg/bupropion 360 mg) QD NB-301 (No DM)	-6.1	-1.3	-4.8	NDA 200063, ISE Table 18
NB-302 (No DM)	-9.3	-5.1	-4.2	
NB-304 (DM)	-5.0	-1.8	-3.3	

The Division does agree with Orexigen that the blood pressure/pulse safety signal appears to be a greater concern for sibutramine than Contrave.

In the FDA briefing document for SCOUT, we reported a placebo-subtracted change in LDL from SCOUT of +2.7 mg/dl (unfavorable). The placebo-subtracted changes in HDL and TG were 1.1 mg/dl and -3.3 mg/dl, respectively. The lipid changes relative to placebo are more favorable with sibutramine in other, shorter-term studies such as those included in the original NDA (described in next paragraph). SCOUT is the longest study of sibutramine and the placebo-subtracted weight loss over the course of the 3.4 years of follow-up was smaller than that shown in shorter-term studies of younger individuals.

While the favorable lipid effects were not as evident in the SCOUT trial, in the sibutramine trials done for approval (which represent a more similar population to

Contrave than SCOUT) there were favorable lipid effects seen—see attached table from sibutramine label

Sibutramine induced weight loss has been accompanied by beneficial changes in serum lipids that are similar to those seen with nonpharmacologically-mediated weight loss. A combined, weighted analysis of the changes in serum lipids in 11 placebo-controlled obesity studies ranging in length from 12 to 52 weeks is shown below for the last observation carried forward (LOCF) analysis.

Combined Analysis (11 Studies) of Changes in Serum Lipids - LOCF

Category	TG	CHOL	LDL-C	HDL-C
	% (n)	% (n)	% (n)	% (n)
All Placebo	0.53 (475)	-1.53 (475)	-0.09 (233)	-0.56 (248)
< 5% Weight Loss	4.52 (382)	-0.42 (382)	-0.70 (205)	-0.71 (217)
≥ 5% Weight Loss	-15.30 (92)	-6.23 (92)	-6.19 (27)	0.94 (30)
All Sibutramine	-8.75 (1164)	-2.21 (1165)	-1.85 (642)	4.13 (664)
< 5% Weight Loss	-0.54 (547)	0.17 (548)	-0.37 (320)	3.19 (331)
≥ 5% Weight Loss	-16.59 (612)	-4.87 (612)	-4.56 (317)	4.68 (328)

Baseline mean values:

Placebo: TG 187 mg/dL; CHOL 221 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL

Sibutramine: TG 172 mg/dL; CHOL 215 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL

TG: Triglycerides, CHOL: Cholesterol, LDL-C Low Density Lipoprotein-Cholesterol

HDL-C: High Density Lipoprotein-Cholesterol

Comment #3 (page 3 of 7-14-2011 document):

As was stated earlier, the Contrave data met the minimal categorical weight-loss efficacy criterion yet was coupled with a blood pressure/pulse safety signal and insufficient cardiovascular data. Sufficient CV data is necessary to ensure that Contrave-induced weight loss translates either into a quantifiable CV benefit, or, at a minimum, an acceptable degree of CV risk.

Orexigen states that antidepressants are used for the symptomatic treatment of major depressive disorder, yet are known to exacerbate the risk of suicidality. This risk is managed through patient selection, labeling, and a Risk Evaluation and Mitigation Strategy (“REMS”). This reviewer contends that we should have some estimate of the CV risk, if any, given the questionable benefit-to-risk profile of Contrave and the negative results of SCOUT. Furthermore, managing the risk through patient selection—limiting its use to patients without diabetes or CVD—as proposed by Orexigen—is not logical, as that population is a main treatment target for weight-loss agents.

Comment #4 (page 5 of 7-14-2011 document): The claim of ^{(b) (4)} weight loss with a reduction in blood pressure is post-hoc and best-case scenario in nature by virtue of only

looking at the subjects who fit this criteria at the end of the trial—not as prospectively designed in the protocol. Refer to comment #22 for additional information.

Comment #5 (page 6 of 7-14-2011 document):

Orexigen has presented no data that these labeling restrictions would actually result in the exclusion of subjects at higher risk, such as patients with diabetes or cardiovascular disease. Additionally, these patients make up a significant portion of the target patient population and it is counter-intuitive to exclude them from use. Lipid-lowering drugs are also given to lower a surrogate marker (LDL-C) which has been shown through multiple CV outcomes trials to decrease patients' risk for cardiovascular disease. We would not entertain restricting the target patient population to those without diabetes or CVD with a lipid-altering agent and a similar rationale exists for drugs indicated to treat obesity—where one of the primary goal is to reduce cardiovascular disease.

Comment #6 (page 2 of 6-08-2011 document):

EMDAC Vote: source (pgs 374-425)

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drug/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM239926.pdf>

Of note, 2 of the 11 panelists (Hirsch, Felner) who voted in favor of conducting the cardiovascular trial post-approval, voted “no” to the question of whether the potential benefits of NB outweigh the potential risks. One could argue that the 11 post-approval CV trial votes vs 8 pre-approval CV trial votes translates into 9 for post-approval trial and 10 for pre-approval trial.

In addition, several of the panelists (Hiatt, Thomas, Felner, Morrato, Hirsch) who voted for a post-approval trial struggled with that issue but indicated that one of the reasons they ultimately voted for a post-approval trial was because they felt a pre-approval requirement would greatly discourage further drug development. Additionally, several members commented that the post-approval study needed to be started promptly, potentially before approval is given (Thomas) with very clear timelines for implementation and milestones because of the observed safety signal (Goldfine, Morrato).

Of the 13 members that voted that the benefits outweighed the risk, 3 members (Balish², Seely, Spruill) voted for a pre-approval CV trial. One could argue that this translates into 10 members voting that the data “as is” is sufficient for approval and 10 voting for additional CV data prior to approval.

Dr. Rogawski, who voted ‘yes’ to the benefit vs risk question, stated the following (pg 419-421): “I voted yes, but with a major, major caveat. I feel that the sponsor fulfilled the

² (transcript pg 407-408) Dr. Marshall Balish voted that the benefits outweighed the risk and commented that it was inconsistent with his prior vote. His primary reason for wanting a preapproval study was that the study be definitely done so that we could define those risks. He was somewhat reassured by the FDA's statement about their commitment to have that study going forward.

requirements set by the FDA in terms of the study. The results met the criteria. And I think it would be a bad message to the industry to change in midstream the requirements. On the other hand, I feel this is a flawed product. I think it should only be used in very special circumstances. I think that my concern relates not only to the cardiovascular risk, but particularly to the seizure risk. I think it's not inconsequential. I feel that, as a committee, we didn't pay enough attention to that... Just to reinforce my concern about not wanting this to be perceived as a first or even second line agent, I had the opportunity to participate as a consultant to this committee in the deliberations regarding phentermine and topiramate. That particular combination agent had much greater efficacy, almost twice the efficacy of this particular combination, and it was in association, of course, with an anticonvulsive drug that doesn't cause seizures. So that would certainly be an agent that I would pick before this one."

Thus, the votes are much more complicated than the simple number comparison.

Those individuals who voted that a study needed to be done preapproval, were Dr. Balish, Dr. Kaul, Dr. Spruill, Dr. Bittner, Dr. Proshan, Dr. Weide, Dr. Heckbert, Dr. Seely. (8)

Those who voted that a study needed to be done post-approval, were Ms. Coffin, Dr. Gardner, Dr. Hiatt, Dr. Oakes, Dr. Felner, Dr. Goldfine, Dr. Hirsch, Dr. Thomas, Dr. Flack, Dr. Hendricks, Dr. Morrato. (11)

Those individuals who voted that the benefits outweighed the risks were Dr. Balish, Ms. Coffin, Dr. Flack, Dr. Gardner, Dr. Goldfine, Dr. Hendricks, Dr. Hiatt, Dr. Morrato, Dr. Oakes, Dr. Rogawski, Dr. Seely, Dr. Spruill, and Dr. Thomas (13)

Those individuals who voted that the benefits did not outweigh the risks were Dr. Bittner, Dr. Felner, Dr. Heckbert, Dr. Hirsch, Dr. Kaul, Dr. Proshan, and Dr. Weide (7).

Comment #7) (page 3 of 6-08-2011 document):

DMEP stated that we would consider approval of Contrave based on interim data from a cardiovascular safety trial that incorporated and satisfied the below recommendations and criteria.

- We recommend that the population enrolled have an estimated annual placebo MACE rate of at least ~ 1.0 to 1.5%. This would necessitate enrolling some patients with a history of cardiovascular events and known risk factors, such as diabetes of substantial duration.
- The interim analysis must be done after > 50% of planned events have accrued and a reasonable portion of study participants have been treated for one year or more.
- The point estimate of the hazard ratio for MACE at the interim analysis must be close to or below unity with an upper bound of the 95% confidence interval that rules out 10 excess MACEs per 1000 person-years.
- The point estimate of the hazard ratio at the final analysis should be close to or below unity with an upper bound of the 95% confidence interval that rules out approximately 7 excess MACE per 1000 subject-years.

- The interim and final results of the primary outcome analysis should meet the above criteria for both the ITT and Per-Protocol populations (as defined below).

In the meeting discussion we stated that the trial guidelines that we sent to Orexigen are a reflection of the SCOUT trial and the number of excess events that led to sibutramine being withdrawn from the market. Sibutramine was removed from the market due in large measure because the results of SCOUT indicated that the drug was associated with 3-4 excess major cardiovascular events per 1000 person years (HR 1.16), with an upper bound of the 95% CI consistent with ~ 7 excess events per 1000 person years (in the ITT population). The point estimate of the hazard ratio and the upper bound of the 95% CI were associated with ~ 5-6 and 9-10 excess events, respectively, in the per protocol or on-drug population. These numbers informed our recommendations regarding acceptable upper bounds at interim and final analyses of your proposed CV safety trial. We also reiterated our belief that the point estimate of risk at the interim and final analysis would need to be near unity.

Among other things, Orexigen asked about both the intent-to-treat (ITT) and per-protocol (PP) populations meeting the criteria for the interim and final results of the primary outcome analysis. FDA asked what the estimate is for subjects that will be off-study drug by the end of the trial. Orexigen estimated that 50-60% of subjects will be on active treatment at one year and that 36-38% of subjects will be on active treatment by the end of the trial. Orexigen asked if they could power the study for the ITT population as the primary analysis population and the PP population would need to be consistent with the ITT population. FDA responded that this would be acceptable.

In summary:

- At this time, SCOUT has established a benchmark for an unacceptable level of excess major cardiovascular events for an obesity drug with sympathomimetic properties.
- A general advisory committee meeting on CV outcomes trials for drugs indicated to treat obesity will be planned for 2012.
- An annual MACE of (b) (4) in the control group might lead to a false sense of security and is not informative data. FDA will need to see an adequate number of CV events in order to evaluate the benefit-to-risk profile of Contrave.
- Efficacy thresholds in the 2007 Guidance should be accompanied by expected biomarker benefit—for Contrave, the fact that blood pressure and pulse did not track with the other benefits is concerning.
- The interim analysis for approval should be conducted after observing 50% or more of the total events—this is necessary due to the lower number of events and a reluctance to make an approval decision without sufficient data.
- The study can be powered for the ITT population but the PP results need to be consistent and not divergent from the ITT results; thus powering for only the ITT population may result in an underpowered study for comparisons using the PP population.

Orexigen added at the EOR meeting that it is considering the appeal process for the Complete Response letter for Contrave.

Comment #8) (page 6 of 6-08-2011 document):

Additional information on the modest weight loss of Contrave

The continuous variable of weight-loss efficacy (the difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant) was not met. In all four Phase 3 trials, NB32 produced statistically significant ($p < 0.001$) weight loss in obese subjects, including those with type 2 diabetes mellitus (NB-304), as compared with the placebo group.

- Population without diabetes:
 - Mean placebo-subtracted weight loss for NB32: 4.2-4.8%
- Population with diabetes:
 - mean placebo-subtracted weight loss for NB32: 3.3%

However, the difference was $< 5\%$.

The categorical variable of weight-loss efficacy (the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant) was met in 2 of 3 trials adequately designed to assess efficacy with up to one year of treatment.

Comment #9) (page 7 of 6-08-2011 document):

In contrast to the applicant's comment that in 3 of the 4 trials, ~ 3-times as many CONTRAVE-treated subjects as placebo subjects experienced at least 5% weight loss—only one trial (NB-301) achieved this. NB-303 is excluded due to the design issues described below. NB-302 did not meet this 3x criterion. NB-304 would have had to achieve 56.7% responders but only achieved 44.5%—this is 2.4x the placebo group % of 18.9%.

	Treatment group	Number (%) of 5% responders
NB-301 Week 56	Placebo	84 (16.4%)
	NB16	186 (39.5%)
	NB32	226 (48.0%)
NB-302 Week 56	Placebo	82 (42.5%)
	NB32	320 (66.4%)
NB-303* Week 28	Placebo	80 (17.5%)
	NB32	459 (55.6%)
NB-304 Week 56	Placebo	30 (18.9%)
	NB32	118 (44.5%)

*In NB-303, because some subjects were re-randomized prior to Week 56, it is difficult to draw accurate conclusions about the long-term efficacy of NB32 from this trial. The Week 28 data, and not the Week 56 data, is considered the primary endpoint in this trial.

Comment #10) (page 7 of 6-08-2011 document):

The changes in HDL and triglyceride levels were small. The decrease in hsCRP was statistically significant in only one trial.

- Waist circumference change from baseline to endpoint.
 - The decrease in waist circumference seen with NB (16 and 32) was greater than placebo in all 4 trials and statistically significant in 3 of the 4 trials based on CTP rules (2.1 to 3.8 cm difference from placebo, LSMean)
- Lipid parameters (HDL, LDL, triglycerides) change from baseline to endpoint.
 - HDL: The LSMean treatment differences from placebo ranged from an increase of 2.6 to 3.5 mg/dL.
 - Triglycerides: The decrease in TG was 8% in NB16, ranged from 7 to 17% for NB32, and 0.8 to 8.5% for placebo. The treatment difference from placebo ranged from 5 to 10%.
 - LDL: Subjects who received NB treatment showed small decreases from baseline in fasting LDL cholesterol which, in general, was not statistically different from placebo. The LSMean treatment differences from placebo ranged from a decrease of 0.4 to 4.4 mg/dL.
- High-sensitivity C reactive protein (hs-CRP)
 - NB subjects showed a greater percentage decrease from baseline in hs-CRP compared with placebo—this was statistically different from placebo in only Trial NB-301 [LS % change from baseline (mg/L): Pbo (-17); NB16 (-28); NB32 (-29)]
- At endpoint, subjects receiving NB32 had statistically significantly greater decreases from baseline in HbA1c (LS mean change NB32 -0.63% vs. -0.14% for placebo; p<0.001).

Comment #11) (page 7 of 6-08-2011 document):

Weight-related quality of life “improvements” were not clinically meaningful.

- Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire
 - The results of the IWQOL- Lite questionnaire total score showed a statistically significant difference in the total score associated with NB (16 and 32) treatment compared with placebo for Trials NB-301, NB-302, and NB-303 but not for Trial NB-304. However, none of the trials showed a clinically meaningful difference between NB and placebo in the IWQOL-Lite total score.

The SEALD review team concluded that the information submitted as part of this NDA fails to document that the IWQOL-Lite is a well-defined and reliable endpoint measure according to the standards set forth in the FDA Guidance for Industry— Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

Comment #12) (page 7 of 6-08-2011 document):

Percentage of subjects with depression or diabetes was small (~10%) and percentage of subjects with CVD was <1%.

NB subjects :

24% (780) with HTN;

10% (333) with DM;
54% (1753) with dyslipidemia;
11% (353) with depression;
0.9% (30) with cardiac disorders of which 0.3% (9) patients in the NB group had a PMH of myocardial infarction

Comment 13) (page 8 of 6-08-2011 document):

Figure 1 represents a post-hoc analysis of subjects that have been cherry-picked from the general population (defined as $\geq 5\%$ weight loss within the first 16 weeks of therapy). The mean body weight change for the Contrave group is -11.3% and -8.6% for the Placebo group—representing a placebo-subtracted weight difference of 2.7%. The proportion of Contrave-treated subjects that met the $\geq 5\%$ weight loss within the first 16 weeks of therapy definition is 51% compared to the placebo-treated group at 19%. The blood pressure and heart rate changes are more beneficial for the placebo group while the Contrave group achieves slightly better reductions in HbA1c, TG, HDL and LDL.

The bar graphs from Figures 1 and 2 in Comment #16 show that Contrave subjects need to lose at least 10% of their body weight to achieve meaningful reductions in SBP and DBP.

Comment #14: (page 9 of 6-08-2011 document):

Orexigen describes the BP and P data as compared to baseline values. The FDA focuses on changes in relation to the placebo group—as detailed below.

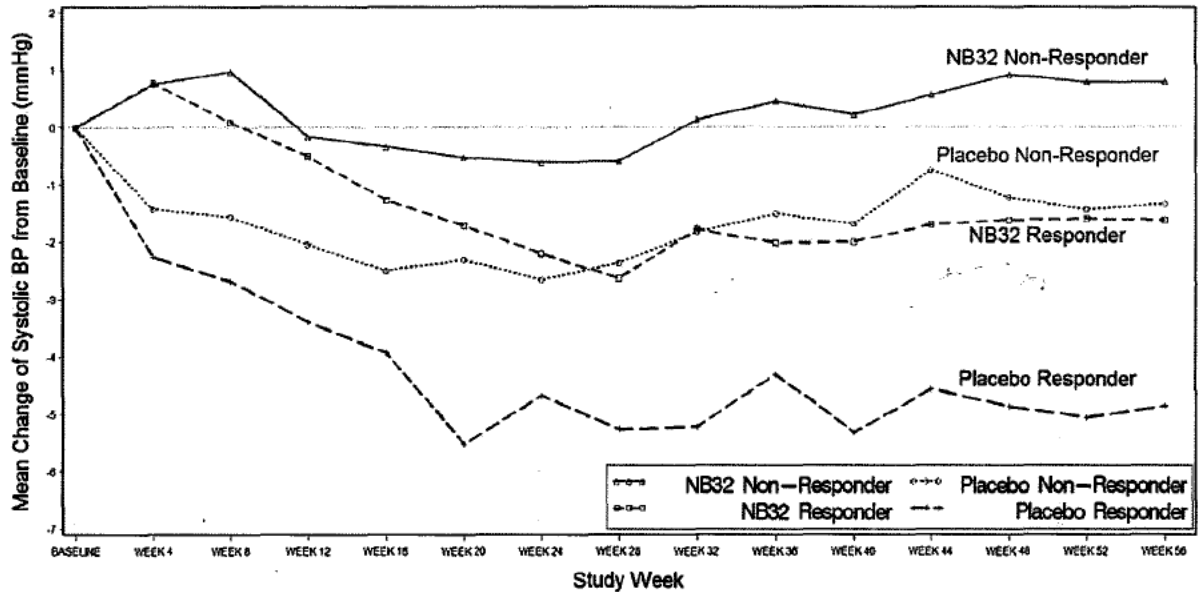
Blood Pressure and Pulse

- A greater percentage of subjects experienced blood pressure and pulse TEAEs in the Total NB group compared with the placebo group (5.9% and 4.2%, respectively). This was primarily attributable to the Hypertension (5.3% Total NB and 4.0% placebo). No serious blood pressure and pulse events were reported.
- In Trial NB-304 (individuals with diabetes), 40 (12.0%) subjects in the NB32 group and 11 (6.5%) in the placebo group had a blood pressure-related TEAE during double-blind treatment. Ten percent (4/40) in the NB32 group were severe compared to none (0/11) in the placebo group.
- *Pulse:*
 - At both Weeks 4 and 8, the Total NB group had a statistically significant difference from placebo of +2.1 bpm.
 - By Week 56, the statistically significant difference from placebo was +1.4 bpm.
 - Increases in pulse from baseline (≥ 5 , ≥ 10 , and ≥ 20 bpm) and pulse increases ≥ 90 bpm at two consecutive or the final visit were observed at higher incidences in NB-treated subjects.
- *Systolic Blood Pressure:*
 - At Week 4 and at Week 8, the Total NB group had a statistically significant difference from placebo of +2.4 mm Hg.

- By Week 56, the statistically significant difference from placebo was +1.5 mm Hg.
- Subjects in the Total NB group were 2.5 x as likely to experience 2 or more SBP readings ≥ 150 mm Hg and were 2x as likely to experience 2 or more SBP readings ≥ 160 mm Hg.
- *Diastolic Blood Pressure:*
 - At Weeks 4 and 8, the Total NB group had a statistically significant difference from placebo of +1.9 and +2.1 mm Hg, respectively.
 - By Week 56, the statistically significant difference from placebo was +1.2 mm Hg.
 - Shifts to high potentially clinically significant (PCS) DBP values were 3 to 4 times more frequent in the Total NB group as compared to Placebo in the first 12 weeks. The incidence remained higher in the Total NB group until Week 28 where the incidence of shifts to high PCS between groups was generally similar between placebo and Total NB until trial end.
- *Ambulatory Blood Pressure*
 - At endpoint (Week 52), the LS mean change in systolic blood pressure was -0.21 mm Hg for Total NB and was -2.82 mm Hg for placebo. The treatment difference was 2.61 mm Hg (95% confidence interval (CI) [-0.33, 5.55]; p=0.081).
 - The LS mean change in diastolic blood pressure in the NB32/48 group was 0.82 mm Hg compared to -2.06 mm Hg in the placebo group and the treatment difference was 2.88 mm Hg (95% CI [0.92, 4.84]; p=0.004).
 - The treatment differences for average daytime ABPM systolic and diastolic blood pressures between the NB 32 group and placebo were systolic: 3.26 mm Hg (p=0.039) and diastolic: 3.06 mm Hg (p=0.007).
 - The treatment differences for average night-time ABPM systolic and diastolic blood pressures between the NB 32 group and placebo were systolic: 0.44 mm Hg (p=0.789) and diastolic: 1.53 mm Hg (p=0.190).
 - The NB32/48 group experienced an LS mean increase in blood pressure load (0.87%) from baseline to endpoint compared to a decrease in the placebo group (-4.09%). The LS mean treatment difference was 4.96% (95% CI [0.97, 8.95]; p=0.015).
 - The treatment difference in the average 24-hour pulse rate for NB32 as compared to placebo was 0.57 bpm (95% CI [-1.81, 2.94]; p=0.635).

The figure below looks at SBP by drug and 5% responder group. Clearly the Placebo Responders had the most favorable SBP changes while the NB32 Non-Responders had the most unfavorable SBP changes.

Figure 1: Change of Systolic Blood Pressure by Treatment Response Group (Completers Population)

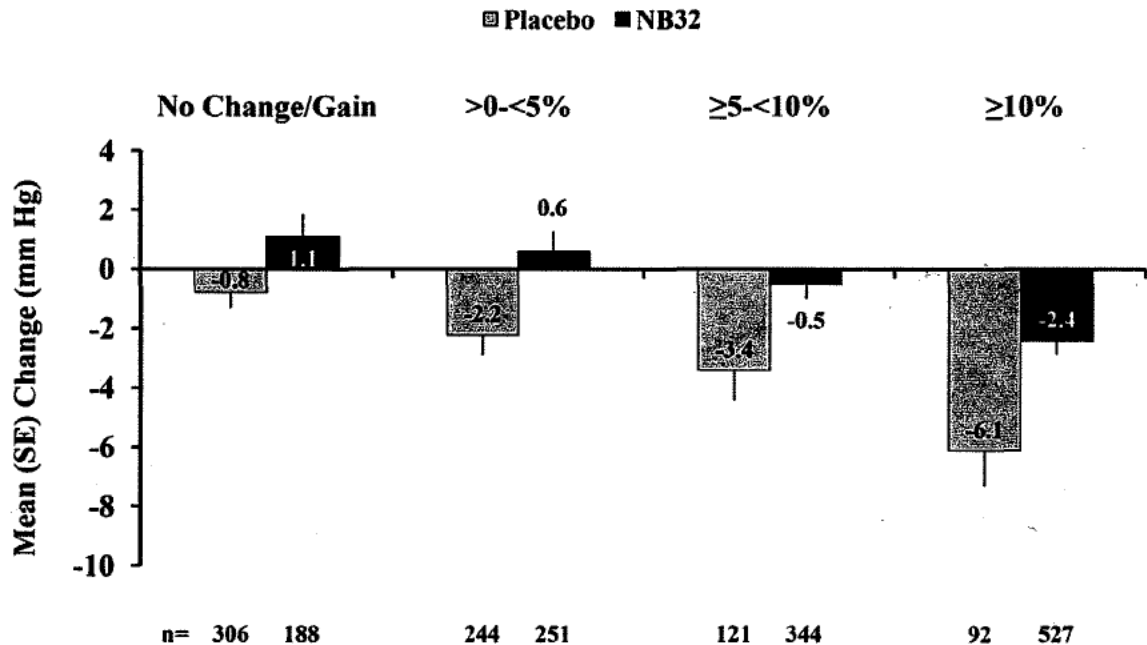


Source: Figure courtesy of FDA Statistical Reviewer Xiao Ding

Responder Analyses by four weight change categories: no change/gain, lose up to 5 percent, lose 5 to 10 %, and lose greater than 10% for NB32 vs Placebo for the Full Analysis Set and for the Completer's Set from baseline to Week 56 for SBP, DBP, pulse, and pressure-rate product were also done to examine the effect of weight loss on vital sign changes.

The bar graph below shows the changes from baseline to endpoint for SBP for each weight response category in the Completer's Dataset. When looking at the Responder analysis of NB subjects who lost at least 5% of their initial body weight reductions from baseline in mean systolic blood pressure were seen. However, this Responder Analysis by four weight change categories shows that subjects who lose <5% body weight experience an increase SBP and subjects do not achieve a meaningful decrease in SBP until they have lost $\geq 10\%$ weight loss (-2.4 mm Hg). Of note, placebo subjects, regardless if they gain or lose weight, experience a decrease in SBP.

Figure 2: Change in SBP at Endpoint by Endpoint Body Weight Change (Completers)



Source: Orexigen Figure 27Sep2010 – 1.3.4

Comment #15) (page 10 of 6-08-2011 document):

The Contrave trials excluded subjects with CVD. The trial results, in a population at low baseline risk for CV events, show the following:

Cardiovascular Events

- MACE events (CV death, MI, CVA) occurred in 3 NB patients vs 1 Pbo patient.
- Overall Cardiovascular AEs—including atherosclerotic disease, arrhythmias, and congestive heart failure-- were similar between the Total NB and placebo groups.
- Ischemic CV events were too few in number to adequately assess CV risk in this patient population.

Comment #16) (page 15 of 6-08-2011 document):

Figure 5 compares 12-week ABPM data for sibutramine with 52-week ABPM data for Contrave.

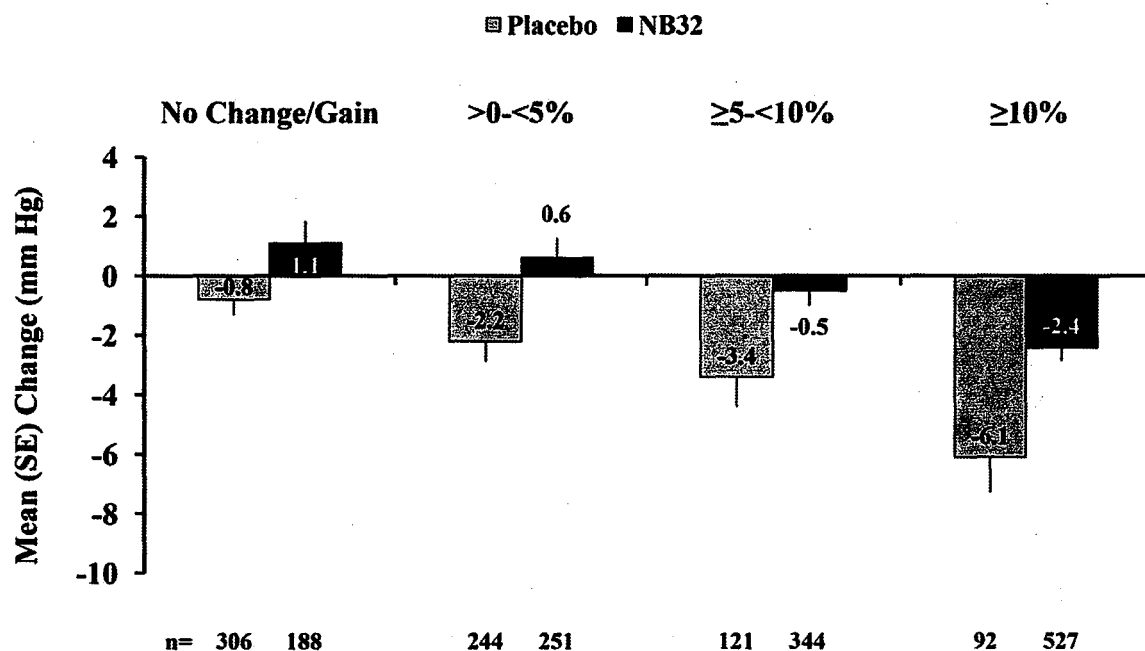
Orexigen comments, “the CONTRAVE Phase 3 program documented a strong relationship between the magnitude of weight loss and reductions in blood pressure.”

As shown in the following two bar graphs, subjects treated with Contrave do not achieve a meaningful decrease in SBP or DBP until they have lost ≥ 10% weight loss.

The bar graph below shows the changes from baseline to endpoint for SBP for each weight response category in the Completer's Dataset. This Responder Analysis by four weight change categories shows that subjects who lose <5% body weight experience an increase SBP and subjects do not achieve a meaningful decrease in SBP (-2.4 mm Hg) until they have lost $\geq 10\%$ weight loss. Of note, placebo subjects, regardless if they gain or lose weight, experience a decrease in SBP.

Looking at the subjects that experience ≥ 2 mm Hg decrease in SBP—that group represents 527/1310 or 40% of NB32 completers as compared to 457/763 or 60% of Placebo completers.

Figure 1: Change in SBP at Endpoint by Endpoint Body Weight Change (Completers)

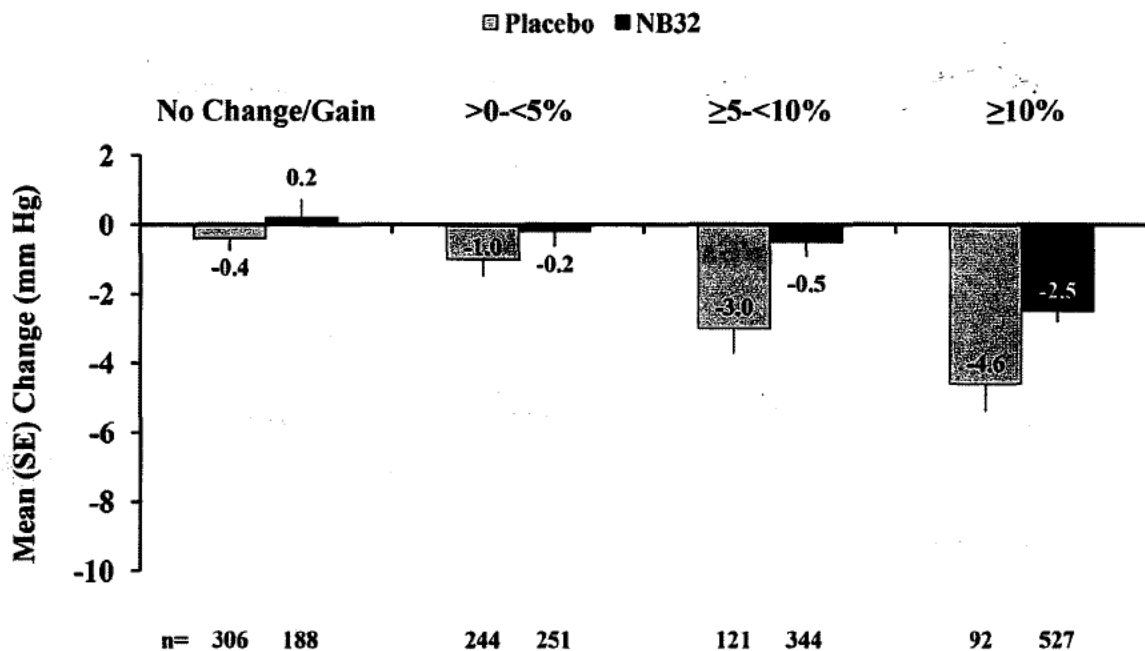


Source: Orexigen Figure 27Sep2010 – 1.3.4

The bar graph below shows the changes from baseline to endpoint for DBP for each weight response category in the Completer's Dataset. Similar to what was seen with SBP, this Responder Analysis by four weight change categories shows that subjects do not achieve a meaningful decrease in DBP (-2.5 mm Hg) until they have lost $\geq 10\%$ weight loss. Of note, placebo subjects, regardless if they gain or lose weight, experience a decrease in DBP.

Looking at the subjects that experience ≥ 1 mm Hg decrease in DBP—that group represents 527/1310 or 40% of NB32 completers as compared to 457/763 or 60% of Placebo completers.

Figure 2: Change in DBP at Endpoint by Endpoint Body Weight Change (Completers)



Source: Orexigen Figure 27Sep2010 – 1.3.6

Comment #17) (page 16 of 6-08-2011 document):

Lipid parameters (HDL, triglycerides) change from baseline to endpoint with Contrave were small and of unknown clinical significance.

- HDL: The LS Mean treatment differences from placebo ranged from an increase of 2.6 to 3.5 mg/dL.
- Triglycerides: The decrease in TG was 8% in NB16, ranged from 7 to 17% for NB32, and 0.8 to 8.5% for placebo. The treatment difference from placebo ranged from 5 to 10%.

Comment #18) (page 17 of 6-08-2011 document):

Small changes in hsCRP are of unknown clinical significance. High-sensitivity C reactive protein (hs-CRP) with Contrave

- NB subjects showed a greater percentage decrease from baseline in hs-CRP compared with placebo--this was statistically different from placebo in only Trial NB-301 [LS % change from baseline (mg/L): Pbo (-17); NB16 (-28); NB32 (-29)]

Comment #19) (page 17 of 6-08-2011 document): What Orexigen has identified is a population of patients that IF they followed the proposed label restrictions for a 5% or greater weight loss response and lack of clinically meaningful changes in BP, would likely be at a lower risk from the pressor effects of Contrave. Whether this restricted population would actually achieve a CV benefit from their weight loss with Contrave is not known.

Comment #20) (page 19 of 6-08-2011 document): Orexigen states that avoiding CONTRAVE use in patients with clinically relevant and sustained blood pressure or heart rate increases minimize any theoretical risk. Yet it is theoretical and unknown if such labeling would be effective. Orexigen has provided no data to prove that these labeling restrictions would be effective inside or outside of the clinical trial setting.

Comment #21) (page 19 of 6-08-2011 document): Table 3 represents a post-hoc, non-randomized, cherry-picked population. The Contrave group achieves slightly greater weight loss (placebo-subtracted difference of 2.8%) in exchange for decreased reductions in SBP, DBP, and heart rate.

Comment #22) (page 23 of 6-08-2011 document): Orexigen's Figure 7 (a new analyses of data presented after the CR letter) represents a post-hoc, ideally modeled population (defined as the ultra low CV risk population of patients who achieve $\geq 5\%$ weight loss within the first 16 weeks of therapy plus no clinically relevant changes in blood pressure or pulse). The mean body weight change for the Contrave group is -12.1% and -9.1% for the Placebo group—representing a placebo-subtracted weight difference of 3%. The proportion of Contrave-treated subjects achieving these post hoc criteria is 46% compared to the placebo-treated group at 19%. The blood pressure and heart rate changes are more beneficial for the placebo group while the Contrave group achieves slightly better reductions in HbA1c, TG, HDL and LDL.

Again, whether this restricted population would actually achieve a CV benefit from their weight loss with Contrave is not known. Of note, this population excludes subjects with Type 2 DM who typically have a smaller amount of weight loss with obesity agents. For Contrave, the trial done in subjects with T2DM achieved a mean placebo-subtracted weight loss of 3.3% compared to 4.2-4.8% achieved in the trials in subjects without diabetes.

Comment #23) (page 24 of 6-08-2011 document): In our assessment, Contrave subjects need to lose at least 10% of their body weight to achieve meaningful reductions in SBP and DBP. In this population, Contrave would likely yield the weight-loss efficacy margin that would allow an acceptable safety trade-off consideration given the adverse blood pressure and heart rate signals.

Figure 8 (a new analyses of data presented after the CR letter) looks at this population (defined as the ultra low CV risk population of patients who achieve $\geq 10\%$ weight loss

within the first 16 weeks of therapy plus no clinically relevant changes in blood pressure or pulse). The mean body weight change for the Contrave group is -16.7% and -14.8% for the Placebo group—representing a placebo-subtracted weight difference of 1.9%. The proportion of Contrave-treated subjects achieving these post hoc criteria are 18% compared to the placebo-treated group at 6%. The blood pressure and heart rate changes are more beneficial for the placebo group while the Contrave group achieves slightly better reductions in TG and HDL. The Contrave population that achieves this degree of weight loss represents <20% of an already highly-selected clinical trial population.

Comment #24) (page 24 of 6-08-2011 document):

“Across the entire Phase 3 program, the average weight loss from baseline was approximately (b) (4)

Please refer to table 38 below from the primary MO review—average weight loss from Contrave across 4 studies is 6.73% and from placebo is 2.53%—a difference of 4.2%. Data is usually presented as placebo subtracted:

- Population without diabetes:
 - Mean placebo-subtracted weight loss for NB32: 4.2-4.8%
- Population with diabetes:
 - mean placebo-subtracted weight loss for NB32: 3.3%

Table 38: Primary Efficacy Analysis in Phase 3 Trials

Trial NB-301: Week 52 was primary endpoint	NB16	NB32	placebo	Total
1. Randomized	578	583	581	1742
Completed 52 weeks	284 (49.1%)	296 (50.8%)	290 (49.9%)	870 (49.9%)
Withdrawn before 52 weeks	294 (50.9%)	287 (49.2%)	291 (50.1%)	872 (50.1%)
FAS population	471	471	511	1453
2. Baseline mean in kg (SD)	100.1 (14.4)	100.2 (16.3)	99.3 (14.3)	
3. % change from baseline, LS Mean (SE)	-5.0 (0.3)	-6.1 (0.3)	-1.3 (0.3)	
Difference from placebo, LS Mean (95% CI)	-3.7 (-4.5, -2.9)	-4.8 (-5.6, -4.0)		
p-value	<0.001	<0.001		
4. No. (%) of 5% responders	186 (39.5%)	226 (48.0%)	84 (16.4%)	
Odds ratio vs. placebo (95% CI)	3.4 (2.5, 4.6)	4.9 (3.6, 6.6)		
p-value	<0.001	<0.001		

Trial NB-302: Week 52 was primary endpoint (intensive lifestyle intervention)	NB32	placebo	Total
1. Randomized	591	202	793
Completed 52 weeks	342 (57.9%)	118 (58.4%)	460 (58.0%)
Withdrawn before 52 wks	249 (42.1%)	84 (41.6%)	333 (42.0%)

FAS population	482	193	675
2. Baseline mean in kg	100.7 (15.4)	101.9 (15.0)	
3. % change from baseline, LSMean (SE)	-9.3 (0.4)	-5.1 (0.6)	
Difference from placebo, LSMean (95% CI)	-4.2 (-5.6, -2.9)		
p-value	<0.001		
4. No. (%) of 5% responders	320 (66.4%)	82 (42.5%)	
Odds ratio vs. placebo (95% CI)	2.9 (2.0, 4.1)		
p-value	<0.001		

Trial NB-303: Week 28 was primary endpoint	NB32	placebo	Total
1. Randomized	1001	495	1496
Completed 52 weeks	538 (53.7%)	267 (53.9%)	805 (53.8%)
Withdrawn before 52 wks	463 (46.3%)	228 (46.1%)	691 (46.2%)
FAS population	825	456	1281
2. Baseline mean in kg	100.7 (16.7)	99.3 (16.0)	
3. % change from baseline, LSMean (SE)	-6.5 (0.2)	-1.9 (0.3)	
Difference from placebo, LSMean (95% CI)	-4.6 (-5.2, -3.9)		
p-value	<0.001		
4. No. (%) of 5% responders	459 (55.6%)	80 (17.5%)	
Odds ratio vs. placebo (95% CI)	6.6 (5.0, 8.8)		
p-value	<0.001		

Trial NB-304: Type 2 diabetes, Week 52 was primary endpoint	NB32	placebo	Total
1. Randomized	335	170	505
Completed 52 weeks	175 (52.2%)	100 (58.8%)	275 (54.5%)
Withdrawn before 52 weeks	160 (47.8%)	70 (41.2%)	230 (45.5%)
FAS population	265	159	424
2. Baseline mean in kg	106.4 (19.1)	105.0 (17.1)	
3. % change from baseline, LSMean (SE)	-5.0 (0.3)	-1.8 (0.4)	
Difference from placebo, LSMean (95% CI)	-3.3 (-4.3, -2.2)		
p-value	<0.001		
4. No. (%) of 5% responders	118 (44.5%)	30 (18.9%)	
Odds ratio vs. placebo (95% CI)	3.4 (2.2, 5.5)		
p-value	<0.001		

Sources: ISE Tables 3-8, 10, 12, 13, Tables ISE.301.1-1, ISE.302.1-1, ISE.303.1-1, ISE.304.1-1 and efficacy tables from FDA Statistical Reviewer J. Derr.
FAS= Full Analysis Set
Results are based on last-observation-carried-forward (LOCF) method while on study drug.

Comment #25) (page 25 of 6-08-2011 document):

Contrave has one-year efficacy data. SCOUT represents efficacy data over ~3.5 years in a much higher-risk population. It remains to be seen what the long-term efficacy of Contrave is.

Comment #26) (page 27 of 6-08-2011 document):

Orexigen comments “The SCOUT point estimate of 1.16 relative risk and upper limit of the CI of 1.31 relative risk applied to a 0.2% background rate obese population results in approximately 0.3 and 0.6 excess events, respectively, per 1000 patient-years of exposure. This falls well below the threshold of 1 to 2 excess events per 1,000 patient-years that the Division, at the EOR meeting, suggested could be acceptable for approval.”

Allowing approval of a drug to treat obesity restricted to a population at low risk for CV events (0.2% background rate) would be difficult to achieve through labeling, would require an onerous restricted distribution ETASU/REMS, and, more importantly, counter-intuitive to the treatment of such a wide-spread disease/condition as obesity and a concerning precedent to set.

Comment #27) (page 27 of 6-08-2011 document):

Orexigen’s statement misrepresents the Division’s view. The issue is that while we know that obesity shortens live expectancy, it is not exactly clear whether weight loss, especially modest weight loss, such as that observed with Contrave, may enhance life expectancy or exert favorable impact on cardiovascular mortality or morbidity. The data at hand are insufficient to directly adjudicate the cardiovascular risk of Contrave, but there are blood pressure and the heart rate signals as well as the concerning data from the bupropion study in smokers that was referred to earlier.

The Division believes that it is essential to ensure that we are not increasing the cardiovascular risk of those exposed to this drug. A CV outcomes trial is necessary to allow us to draw a reliable inference about cardiovascular risk.

Comment #28) (page 30 of 6-08-2011 document):

Efficacy is viewed against the background of safety concerns for the drug or drug class. Achieving the minimal efficacy thresholds spelled out in the 2007 draft guidance satisfies the efficacy component—it does not mean that the safety component is not part of the overall benefit-risk equation. Rimonabant also met the efficacy criteria but was not approved because of psychiatric/suicidal concerns.

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/s/

EILEEN M CRAIG
08/16/2011

ERIC C COLMAN
08/16/2011

8-11-12



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 200063

ACKNOWLEDGE DISPUTE APPEAL AND MEETING GRANTED

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines, Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.

We acknowledge receipt on August 7, 2012, of your request for formal dispute resolution concerning the pre-approval requirement, cited in our January 31, 2011, complete response letter, for a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. We refer to your formal dispute resolution request, received on June 8, 2011, to the Office of Drug Evaluation II (ODE II), and the denial of the appeal by Dr. Curtis Rosebraugh, Director, ODE II on July 7, 2011. We also refer to your formal dispute resolution request, received on July 14, 2011, to the Office of New Drugs (OND), and the denial of the appeal by Dr. John Jenkins, Director, OND on Sept 15, 2011.

Your appeal has been forwarded for review to Douglas Throckmorton, M.D, Deputy Director, Center for Drug Evaluation and Research. In your appeal you request a meeting to discuss the matter. We are granting your meeting request and have scheduled the following meeting.

Date: September 6, 2012
Time: 9:00 am – 10:30 am, EST
Location: 10903 New Hampshire Avenue
White Oak Building #21, Conference Room 1539
Silver Spring, MD 20903

CDER participants (invited):

Center for Drug Evaluation and Research
Douglas Throckmorton, M.D., Deputy Center Director
Robert Temple M.D., Deputy Center Director for Clinical Sciences

Office of New Drugs
John Jenkins, M.D., Office Director
RADM Sandra L. Kweder, M.D, Deputy Office Director
Amy Bertha, Team Leader, Regulatory Affairs Team

Khushboo Sharma, Senior Regulatory Project Manager, Regulatory Affairs Team

Office of New Drugs/Office of Drug Evaluation II

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

Leah Ripper, Associate Director for Regulatory Affairs

Mary Parks, M.D., Division Director, Division of Metabolism and Endocrinology Products

Eric Colman, M.D., Deputy Division Director, Division of Metabolism and Endocrinology Products

Eileen Craig, M.D., Medical Officer, Division of Metabolism and Endocrinology Products

Julie Marchick, M.P.H., Supervisory Project Manager, Division of Metabolism and Endocrinology Products

Meghna Jairath, Pharm.D, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products

Office of Translational Science/Office of Biostatistics

Lisa Lavange, Ph.D., Office Director

Thomas Permutt, Ph.D., Director, Division of Biometrics II

J. Todd Sahlroot, Ph.D. Team Leader, Division of Biometrics II

Janice Derr, Ph.D., Statistical Reviewer, Division of Biometrics II

Please e-mail me a list of your attendees at amy.bertha@fda.hhs.gov. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Please use the visitor main entrance in building 22. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Amy Bertha at (301) 796-1647 or Charmaine Johnson at the OND Immediate Office main number (301) 796-0700.

Subsequent to the meeting, we will respond to the formal dispute request within 30 days of the meeting (October 6, 2012). We will contact you should we have any questions or require additional information. If you have any questions please call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Team Leader, Regulatory Affairs Team
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

AMY E BERTHA
08/11/2012

7-28-11



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 200063

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines, Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.

We acknowledge receipt on July 14, 2011, of your July 14, 2011, request for formal dispute resolution concerning the pre-approval requirement, cited in our January 31, 2011, complete response letter, for a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. We also refer to your formal dispute resolution request, received on June 8, 2011, to the Office of Drug Evaluation II (ODE II), and the denial of the appeal by Dr. Curtis Rosebraugh, Director, ODE II on July 7, 2011.

Your appeal has been forwarded for review to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. In your appeal you request a meeting to discuss the matter. We are granting your meeting request and have scheduled the following meeting.

Date: August 16, 2011
Time: 9:30 am – 11:00 am, EST
Location: 10903 New Hampshire Avenue
White Oak Building #21, Conference Room 1537
Silver Spring, MD 20903

CDER participants (invited):

Center for Drug Evaluation and Research
Robert Temple, M.D., Deputy Center Director for Clinical Sciences

Office of New Drugs
John Jenkins, M.D., Office Director
Lina AlJuburi, Pharm.D, Acting Associate Director of Regulatory Affairs
Amy Bertha, Senior Regulatory Health Project Manager

Office of New Drugs/Office of Drug Evaluation II

Curtis Rosebraugh, M.D., Office Director
Leah Ripper, Associate Director for Regulatory Affairs
Mark Parks, M.D., Division Director, Division of Metabolism and Endocrinology Products
Eric Colman, M.D., Deputy Division Director, Division of Metabolism and Endocrinology Products
Eileen Craig, M.D., Medical Officer, Division of Metabolism and Endocrinology Products
Meghna Jairath, Pharm.D, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products

Office of New Drugs/Office of Drug Evaluation I

Norman Stockbridge, M.D., Division Director, Division of Cardiovascular and Renal Products

Office of Translational Science/Office of Biostatistics

Robert O'Neill, Ph.D., Office Director
Edward Nevius, Ph.D., Office Deputy Director
J. Todd Sahlroot, Ph.D., Division Director and Team Leader, Division of Biometrics II
Aloka Chakravarty, Ph.D., Division Director, Division of Biometrics VII
Mat Soukup, Ph.D., Biometrics Team Leader, Division of Biometrics VII
Xiao Ding, Ph.D., Biometrics Reviewer, Division of Biometrics VII

Please e-mail me a list of your attendees at amy.bertha@fda.hhs.gov. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Even though the meeting is scheduled to be held in building 21, please use the visitor main entrance in building 22. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Amy Bertha at (301) 796-1647 or Victor Vail at the OND Immediate Office main number (301) 796-0700.

Subsequent to the meeting, we will respond to the formal dispute request within 30 days of the meeting (September 15, 2011). We will contact you should we have any questions or require additional information. If you have any questions please call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Senior Regulatory Health Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

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MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
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/s/

AMY E BERTHA
07/28/2011



NDA 200063

**FORMAL DISPUTE RESOLUTION –
Appeal Denied**

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Contrave (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets.

Reference is also made to the complete response (CR) letter of January 31, 2011, to you from Dr. Eric Colman, Division of Metabolism and Endocrinology Products (DMEP, the Division), and to your June 8, 2011, Formal Dispute Resolution Request (FDRR), received June 8, 2011.

Your FDRR identifies five issues to be resolved listed below.

- A. *Whether the data in the Contrave NDA provide sufficient information regarding the benefit-risk profile of Contrave to permit approval with appropriate labeling, risk management, and post-approval commitments.*
- B. *Whether the data in the Contrave NDA demonstrate a favorable benefit-risk profile of Contrave in patients without type 2 diabetes, active cardiovascular (CV) disease or non-responders so as to permit approval for this limited population with appropriate labeling, risk management, and post-approval commitments.*
- C. *Whether the requirement for a pre-approval cardiovascular outcomes study for Contrave is consistent with recent FDA actions on similarly situated products.*
- D. *Whether the proposed labeling and REMS can adequately mitigate any potential cardiovascular outcomes risk and thereby alter the risk-benefit profile in a manner sufficient for approval.*
- E. *Whether the efficacy thresholds set forth in the weight loss guidance are consistent with FDA's current view of demonstrating benefit in an overweight or obese population without other co-morbidities.*

You request that “FDA reconsider the requirement for a pre-approval CV outcomes trial in the context of the specific benefit, risk, unmet need, and proposed risk mitigation strategy that were provided to the NDA.” You also request that “FDA reconsider this requirement, at a minimum, for the narrowed population excluding patients with type 2 diabetes or active CV disease.”

I have reviewed the information you provided in support of your request. I have consulted with staff from DMEP, Office of Biostatistics, and Office of Clinical Pharmacology, and with Dr. Robert Temple, Deputy Center Director for Clinical Science, and Dr. Robert O’Neill, CDER Statistical Advisor.

I have completed my review of your request for formal dispute resolution and, after careful consideration, deny your appeal. I agree with DMEP that prior to approval you must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to define the risk of major adverse cardiovascular events in overweight and obese subjects treated with Contrave. These data will allow for an informed decision on whether the benefit-risk profile supports marketing. I will summarize the reasoning for my decision below.

Before I address the issues above, I will summarize the weight loss and blood pressure results from your trials. Below are the placebo-subtracted means across your various trials. The Draft Guidance for Industry *Developing Products for Weight Management*¹ recommends that a product can be considered effective for weight management if, after one year of treatment, either a mean or a categorical benchmark is met. The table below of your clinical trials demonstrates that Contrave did not meet the efficacy benchmark variable of mean weight-loss efficacy, defined as 5% mean difference between active- and placebo-treated groups.

Study	LS Mean Difference from Placebo
NB-301	-4.8
NB-302	-4.2
NB-303	-4.6
NB-304*	-3.3

*Obese subjects with type 2 diabetes

Two of three 56-week trials were adequately designed to assess categorical efficacy and met that variable of weight-loss efficacy, defined as the proportion of subjects who lose greater than or equal to 5% of baseline body weight being at least 35% and approximately double the proportion in the placebo-treated group.

¹ Draft Guidance for Industry, *Developing Products for Weight Management*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf>

Study	Treatment group	Number (%) of 5% responders
NB-301 Week 56	Placebo	84 (16.4%)
	NB32	226 (48.0%)
NB-302 Week 56	Placebo	82 (42.5%)
	NB32	320 (66.4%)
NB-303* Week 28	Placebo	80 (17.5%)
	NB32	459 (55.6%)
NB-304 Week 56	Placebo	30 (18.9%)
	NB32	118 (44.5%)

*Some subjects in NB-303 were re-randomized prior to Week 56 confounding results. Week 28 data was considered the primary endpoint.

The changes on lipid parameters were small and of unknown clinical significance.

Contrave did meet the benchmark threshold for a demonstration of efficacy (per our draft guidance) on one of the two possible specified criteria. However, this degree of weight loss is modest at best and must be viewed in the context of risks. Weight reductions demonstrated by Contrave are similar (based on cross-study comparisons) to those observed for sibutramine (see addendum). This is important as I will discuss below.

The efficacy results for Contrave must be viewed in the context of the increases in ambulatory blood pressure (placebo-subtracted) of 2.6 mmHg for systolic and 2.9 mmHg for diastolic. Placebo responders (at least 5% weight loss) had the most favorable blood pressure responses while Contrave non-responders (less than 5% weight loss) had the most unfavorable (see addendum). Therefore, Contrave has modest efficacy results while at the same time having a concerning safety signal, increased blood pressure, which is known to increase CV adverse events. The review of your safety database from controlled trials reveals a total of four major adverse cardiac events (MACE, defined as CV death, myocardial infarction, and stroke). Three of these events occurred in subjects receiving Contrave, and one in a placebo subject. Clearly, this is an insufficient number of events upon which to draw any conclusions.

The five issues you identify above are intertwined and I will address them together, making selective comments specific to each one. As was explained to you at the End-of-Review meeting (EOR) on May 26, 2011, our review of the data from the Sibutramine Cardiovascular Outcome Trial (SCOUT)² has influenced our approach to the review of drugs used in the treatment of obesity that also cause increases in blood pressure. Therefore, it is appropriate to review the decision process that led us to request Abbott Laboratories to voluntarily withdraw Meridia (sibutramine) from the United States market,³ and how that decision applies to your application.

² James WP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010 Sep 2;363(10):905-17.

³ Memorandum to the file, NDA 20-632, Meridia (sibutramine hydrochloride monohydrate). October 4, 2010. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM228795.pdf>

Obesity is a chronic disease, the treatment of which is intended to reduce morbidity and mortality, much of which is related to an increased risk of CV events (MACE). Epidemiologic data indicate that even small amounts of diet- or exercise-induced weight loss, if maintained, are associated with CV benefits. Therefore, it has been theorized that drug therapy resulting in weight loss will result in CV benefit. However, this theory has not been confirmed for any weight loss drug, and in the case of sibutramine, patients treated with the drug were actually at an increased risk for CV events. The results of SCOUT showed that active therapy compared to placebo increased the relative risk for MACE by 16% in a population of older overweight and obese individuals. The increase in MACE occurred despite sibutramine thereby demonstrating benefit (in registration trials)⁴ on many of the same cardiometabolic factors that you cite as reasons to allow marketing for Contrave. This result occurred despite the protocol for SCOUT allowing for treatment of increased blood pressure to goal levels below 140/90 mmHg for those without comorbidities and below 130/80 for those with comorbidities, or removal from trial for sustained blood pressure greater than 160/100 (systolic/diastolic). Therefore, despite sibutramine having a favorable effect on weight loss and cardiometabolic risk factors, and allowing for treatment of hypertension, toxic effects due either directly or indirectly to the drug itself led to increased CV harm.

Throughout your FDRR, you refer to substantial evidence of efficacy and the expected clinical benefit that will be the result of Contrave-induced weight loss. However, your reference to benefit is in regard to improving CV surrogates, which the results of SCOUT indicate are dissonant from realizing actual clinical CV benefit if the drug itself may actually cause harm due to increases in blood pressure. There are other examples of drugs demonstrating beneficial changes regarding cardiometabolic factors that ultimately were shown to perhaps not provide CV benefit (fenofibrate) or actually demonstrate CV harm (muraglitazar, torcetrapib). While these examples were not specifically used for the treatment of obesity as was sibutramine, they do indicate that improving cardiometabolic factors (lipid parameters, HbA1c, etc.) may not lead to improvement in CV outcomes. These examples do not diminish the importance of weight reduction or treating other CV risk factors, but the incongruent results raise the possibility that harm may occur and be due to molecule-specific adverse effects (e.g., off-target toxicity), or to the drug's unfavorable effect on some other CV risk factor, such as raising blood pressure (torcetrapib). Throughout your FDRR, you state that Contrave use results in clinically meaningful weight loss; however, this conclusion is based on changes in cardiometabolic parameters, not CV benefit, and the examples above illustrate that these two parameters may be discordant.

Our review of the SCOUT data demonstrated evidence of CV harm without defining a population that may receive benefit. Abbott suggested, much as you are, that labeling could restrict use of sibutramine to a low-risk population, and they speculated that this group may receive CV benefit. We were not able to validate this assumption based on additional exploratory subgroup analyses of the SCOUT trial. While it is true that restricting sibutramine to a group with a very low attributable risk would limit the number of actual CV events (depending

⁴ Based on the results of sibutramine analysis for 11 placebo-controlled studies ranging from 12 to 52 weeks upon which approval and labeling was based. The 11 trials are similar in length and patient population to those studied for Contrave. This is presently the most appropriate cross-study comparison as we do not have the same time of exposure with Contrave to determine cardiometabolic factors trends with extended exposure.

upon the amount of relative increase should it occur), we determined that absence of risk even in this group was not proven, and Abbott would have to identify a population in whom the risk-benefit ratio was favorable (i.e., there was not CV harm but actual benefit or at least convincing evidence of lack of harm). Also, while Abbott had suggested restricting sibutramine only to those that had actual weight loss (responders), the subgroup that demonstrated a lower risk of CV events compared to non-responders, this same effect was also seen in the placebo group (i.e., lower risk of CV events in placebo responders versus placebo non-responders). Comparison of sibutramine responders versus placebo responders revealed higher CV event rates in sibutramine responders, demonstrating that sibutramine use still had unfavorable CV effects despite weight loss (when compared to equivalent weight loss for the placebo group). So, we determined that trying to restrict the use of sibutramine only to patients who responded, or to those with low CV risk, with the concept that there may actually be CV benefit, was at best an unproven hypothesis and would need evidence to allow continued marketing. Considering the overlap in patients with obesity, type 2 diabetes mellitus, and CV disease, it was not possible based on the SCOUT trial to tell if there was a threshold cut-point, or population, where the CV benefit from weight loss would exceed the risk from the intrinsic harmful CV effect of sibutramine, felt to be on the basis of increasing blood pressure (perhaps as a result of increased sympathetic tone). While other potential benefits of weight loss, such as reductions in obstructive sleep apnea, obesity-related cancers, or prevention of type 2 diabetes are important, they had not been shown with the use of sibutramine (or Contrave either) that would justify its continued use.

Therefore, we do have regulatory background and precedence that can be directly applied to the review action for Contrave. The main concern with Contrave is the clinical demonstration of increase in blood pressure (perhaps from increased sympathetic tone) from the bupropion component. This increase does not seem to be of the same character/extent as the increase with sibutramine (noting that there have not been any direct comparisons). However, much like sibutramine, it is unknown if there is a threshold cut-point or population where the CV benefits from weight loss would exceed the potentially harmful CV effects secondary to bupropion-induced blood pressure elevations. Therefore, even if the hypertensive effect with Contrave is less pronounced than that observed with sibutramine (not proven), you have not demonstrated that there is a threshold weight loss that would overcome the adverse CV effects of blood pressure increase. I find DMEP's review and action regarding sibutramine directly relevant, applicable, and consistent with the CR action taken for Contrave and requirement of a pre-approval CV outcome trial.

You question whether the requirement for a pre-approval CV study for Contrave is consistent with recent FDA actions on similarly situated products. You state that bupropion is approved for other indications (without the requirement of a CV outcome study) and therefore the risk-benefit profile that led to these approvals is applicable to your application. Bupropion is approved for major depressive disorder. This is not an analogous comparison and is not "similarly situated" to Contrave use for weight maintenance. Treatment for major depression has different elements to consider (i.e., disease being treated, other available interventions) in assessing risk-benefit than those that are considered for obesity. This is especially pertinent as one of the primary intents of using drugs in the treatment of obesity is to decrease the risk and incidence of CV events (as compared to using drugs in the treatment of depression). Therefore, it would be paradoxical to institute drug therapy with the intent of decreasing CV events if the treatment actually increased

such events. Thus, the case cited by you above as similarly situated is not such a case, as bupropion is being used to treat depression and is not being used in a condition with the intent of decreasing CV disease. This concept also applies to the other drugs you reference that have increases in blood pressure (duloxetine, milnacipran) as they are indicated for different conditions and have considerations in a risk-benefit analysis that are quite different from Contrave use for weight management.

You also assert that the safety of bupropion is well characterized, having been approved for over 20 years, and that the postmarketing safety profile does not reveal a signal of adverse CV outcomes. The length of marketing and lack of postmarketing reporting is not reassuring in this regard as passive drug safety reporting systems are not well-suited to assess whether a drug increases the risk of a commonly occurring adverse event. You also refer to the use of bupropion in the treatment of smoking cessation. Bupropion, used as an aid for smoking cessation, is not necessarily a chronic therapy as it is labeled for use for 12 weeks, although treatment up to 6 months is efficacious. However, it is not reassuring that in a small trial of smokers hospitalized for acute CV disease there was a numerical imbalance for adverse CV events associated with bupropion use (incidence ratio= 1.56, CI=0.91, 2.69).⁵ While not statistically significant, this small trial does provide possible evidence of bupropion-induced CV harm with short-term use that must be factored into the safety profile with chronic use. Therefore, without a dedicated long-term CV outcome trial to evaluate bupropion, lack of evidence of a CV risk (when it has not been appropriately evaluated) is not evidence of lack of CV risk. Our decision to now request a CV outcome trial for an anti-obesity drug containing bupropion demonstrates that regulatory science is not static and that the totality of the data must be considered as new information (SCOUT) becomes available. It also is very consistent with our approach to sibutramine, which was used for the same indication that you are seeking.

You question whether the efficacy thresholds in the weight loss guidance are consistent with our current view of demonstrating benefit in overweight or obese populations. You further question the “demands for safety data that exclude exceedingly small levels of risk.” I believe we have been consistent in our review of risk-benefit for obesity drugs as is exemplified by the outcome regarding the rimonabant application for weight loss. Rimonabant had similar weight reduction effects and decreases in cardiometabolic parameters (improvements in levels of triglycerides, HDL cholesterol, and HbA1c in subjects with type 2 diabetes)⁶ as Contrave. In 2007, our review discovered risks for psychiatric adverse events, in particular suicidality (though rare) and depression, that would need to be factored into any risk-benefit analysis. It was also concerning that the data indicating increased incidence of psychiatric and neurologic adverse events in patients treated with rimonabant came from trials excluding patients with major psychiatric and neurologic disorders (much as your trials exclude those at risk for CV events). This raised the possibility that the true risks for rimonabant-induced neuropsychiatric events in the general population may be greater than those observed in the clinical trials. These results would also justify an outcome study to demonstrate actual benefit in the face of actual harm. We have always viewed efficacy against the background of safety concerns for all applications and have

⁵ Rigotti NA, Thorndike AN, Regan S, et al. Bupropion for smokers hospitalized with acute cardiovascular disease. *Am J Med.* 2006 Dec; 119(12):1080-1087.

⁶ Unlike Contrave, subjects receiving rimonabant also demonstrated improvements in blood pressure compared to subjects receiving placebo.

applied this consistently to drugs being developed for weight management. It is also pertinent that rimonabant did not attain marketing status in the United States despite being approved for marketing for weight loss by the European Medicines Agency (EMA). The EMA later withdrew their marketing authorization because the efficacy was deemed not sufficient in light of reports of serious psychiatric events.

Although weight reduction is undertaken for a variety of reasons, overweight and obesity have been widely associated with excess CV risk. For this reason, it stands contrary to the treatment of obesity to consider approval of a drug that may increase the risk of CV disease, especially in light of the results of the SCOUT trial. The above examples should be cautionary that when a concern arises, it needs to be adequately evaluated. Your proposal to evaluate the potential for Contrave to cause CV adverse events after approval is not logical or consistent in regard to our action regarding sibutramine (or rimonabant).

Regarding the CV outcome trial that we require, I cannot opine on your comments regarding the size and feasibility without reviewing specifics of your assumptions. Determining the size of an event-driven non-inferiority trial requires the consideration of many factors including the background rate in the control group, study population, enrichment possibilities, duration of exposure and follow-up (time to get the results), the primary objective of the trial (intent-to-treat or per-protocol) and the parameter assumptions for the hazard ratios of interest. We have not received a formal protocol from you upon which to comment or make further recommendations and have informative discussions. Performing a non-inferiority CV outcome trial in obese patients in light of the results of SCOUT may prove challenging, but I do not think it is impossible and it may not require the number of patients you have cited (depending upon the other factors I have mentioned above and further considerations).

To illustrate this point, it is valuable to review the results of the rimonabant for prevention of cardiovascular events trial (CRESENDO).⁷ At termination, 18,695 patients had been randomized, and the study had a mean follow-up of 13.8 months (planned for 3-5 years). This represents 21,500 patient-years exposure (33 months follow-up would have provided approximately 51,400 patient-years exposure). The trial had planned for 1600 MACE events, of which approximately 739 had been collected at the time of termination. The hazard ratio (HR) for MACE was 0.97 (95% CI= 0.84, 1.12). These results represent a reduction of 0.9 excess events per 1000 patient-years (95% CI= -4.8, 3.6), or approximately one positive outcome, with an upper bound of the 95% CI for the HR which is less than the estimated HR=1.16 demonstrated in SCOUT. It is worth noting that subgroup analysis of the CRESENDO data demonstrated that the greatest CV benefit was demonstrated in subjects with overt vascular disease (N=10,587, HR=0.95, 95% CI 0.80-1.13), a population you expressed reluctance to enroll. Either of these results would clearly fulfill (exceed) the requirements we stipulated to you

⁷ Topol EJ, Bousser MG, Fox KA, et.al. Rimonabant for prevention of cardiovascular events (CRESENDO): a randomized, multicentre, placebo-controlled trial. *Lancet*. 2010 Aug 14;376(9740):517-23.

at your EOR meeting and would require far fewer subjects than what you quoted in your FDRR.⁸ This indicates that our request is not unreasonable and can be accomplished.⁹

(b) (4)

While we do value the advice we receive from advisory committees (AC), their recommendations are advisory and not binding. Most of the time Agency and AC recommendations are congruent, but it is neither rare nor unusual when we come to a different conclusion from the AC majority vote.¹⁰ When there is not congruency with the panel majority vote, it can result in FDA either approving a drug where the panel recommendation was to not approve or the other way around. Voting is more complicated than simply comparing the number of “yes” and “no” responses. You have parsed the voting in a variety of ways and cited selected quotes (out of context) by various panel members to support your position. I do not think it is useful to place too much reliance on the ultimate vote, or parsing what each member may mean by a previous vote. As an example, if one wanted to present an opposing view to yours, three members voted for approval and also voted for a pre-approval CV trial which could be interpreted to mean that 10 members voted that the application was sufficient “as is” for approval and 10 members voted for additional data prior to approval, which would be a deadlock vote with no clear majority. I do not find this type of parsing particularly helpful and instead value a synthesis of the totality of the comments made during the AC meeting which I feel is a better reflection of the certainty or uncertainty members felt. My interpretation of the overall comments made at the AC meeting indicated that many panel members were struggling with a decision and could be swayed one way or another with further reflection.

Summary:

Obesity is a growing epidemic in the United States and a tremendous burden to both the people it affects and the health care system. Epidemiologic data indicate that obesity is associated with a myriad of adverse health outcomes including diabetes, cardiovascular disease, sleep apnea, osteoarthritis, and cancer. The goal of weight management, therefore, is to effect weight loss in obese patients with the goal of decreasing these adverse outcomes and improving quality of life. Since the epidemiologic data indicate that as weight increases the poor outcomes mentioned

⁸ This is in stark contrast to your assertion that the study would require 120,000 subject-years (80% power and more than 100,000 subjects for duration of approximately 3-4 years.

⁹ Figure 3 of the recent publication “Effect of rimonabant on carotid intima-media thickness (CIMT) progression in patients with abdominal obesity and metabolic syndrome: the AUDITOR Trial” by O’Leary et al., Heart 2011;97:1143-1150, also appears to replicate rimonabant having a HR less than 1.0 on MACE events.

¹⁰ How often does the FDA agree with its panels? <http://www.pharmalot.com/2010/10/how-often-does-the-fda-agree-with-its-committees/>

above increase, it would seem intuitive that weight loss will reverse these poor outcomes and can be used as a surrogate to indicate decreases in obesity-related diseases. This may be true for weight loss that is achieved through non-pharmacologic means; however, history has taught us that many marketed weight-loss drugs also had off-target activity that adversely affected some of the outcomes above. These drugs were never able to justify the amount of weight loss they demonstrated in the face of serious (even if rare) adverse events. The Agency is very aware of the obesity epidemic and would desperately like to facilitate the approval of effective therapies for sustained weight management, but we should have little tolerance for potential devastating adverse effects, even if rare, in the face of modest weight loss.

The results from SCOUT and our subsequent action regarding sibutramine have outlined our approach to anti-obesity drugs that have hypertensive effects. The results of SCOUT have set a threshold for what will not be tolerated in regard to CV risk for proposed obesity drugs with hypertensive effects. Your remediation proposals to allow marketing of Contrave (i.e., identification of a population where the theoretical benefit outweighs the theoretical risk, REMS, etc.) were also proposed by Abbott to allow continued marketing for sibutramine and were determined unworkable and inappropriate. Therefore, DMEP's action for Contrave is entirely consistent with our action for sibutramine. For drugs seeking an anti-obesity indication that have a blood pressure effect (or perhaps adverse effect on any other well-established CV risk factor), a rigorous CV evaluation will be required to demonstrate they are under the level of risk that led to the market removal of sibutramine. Alternatively, sponsors developing drugs seeking an anti-obesity claim that increase blood pressure can demonstrate cardioprotection and not just non-inferiority to placebo treatment. You seem to agree in your FDRR letter that the CV risk of Contrave needs to be defined, but question whether this can be done after approval as a postmarketing requirement (PMR). I do not find a compelling reason in your argument for a justification of why you should not demonstrate a neutral (or beneficial) CV risk profile of Contrave before marketing. You request to do a postmarketing CV evaluation while approved for a limited indication for a low risk population, so that if there were an adverse effect, it would be limited in scope. The logical conclusion of this approach is that if it ultimately was proven that Contrave caused harm, we would require removal of the drug, as we did with sibutramine. These same arguments were put forth by Abbott for sibutramine to allow continued marketing and were rejected.

The potential that the results of SCOUT may influence your program should not be a surprise as you were alerted to this early in your development program. This concern was relayed to you on October 1, 2007, during our meeting with you to discuss your phase 3 development program for Contrave.¹¹

“Given that sibutramine, a weight-loss drug also associated with small-to-modest mean increases in systolic and diastolic blood pressure and pulse rate, is currently

¹¹ I mention here that you note that, “In 2007, FDA spurred investment into obesity therapies by clearly defining a clinical development path sufficient to demonstrate efficacy in weight management.” However, later that year was the NDA submission and AC meeting regarding rimonabant. The outcome of this by an objective observer would indicate that efficacy will also be viewed in the context of potential safety issues, as would our response to you in 2007. This demonstrates that there has not been a shift in our thinking regarding “the benefit of weight loss and degree of risk that can tip the balance to non-approvability.”

being evaluated in a large cardiovascular outcome study, it is possible, depending on the blood pressure data to be obtained with your product, that a similar study would be required for a fixed-dose combination of bupropion and Naltrexone.”

The domestic history of approval, and subsequent removal, of drugs or supplements used in weight management serves to be remindful that caution should be exercised, e.g.,

1. phenylpropanolamine and hypertension-induced CV events,
2. ephedra and hypertension-induced CV events,
3. sibutramine and hypertension-induced CV events,
4. fenfluramine and valvulopathy, and
5. dexfenfluramine and valvulopathy.

These all had demonstrated efficacy measured by weight reduction, but adverse cardiac and/or vascular effects prohibited continued marketing in the context of insufficient off-setting benefits. Upon reflection, approving an obesity drug that causes an increase in blood pressure while awaiting an outcome trial to see if the effect is clinically harmful or not, with the idea that we can remove it if it is causing harm, would seem to potentially be repeating the history of sibutramine bringing to mind the George Santayana quote, “Those who cannot remember the past are condemned to repeat it.”

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. This appeal should be sent again through the Center’s Dispute Resolution Project Manager, Ms. Amy Bertha, with a copy to NDA 200063. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647. Questions regarding next steps with the review division should be directed to Ms. Meghna Jairath, 301-796-4267.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

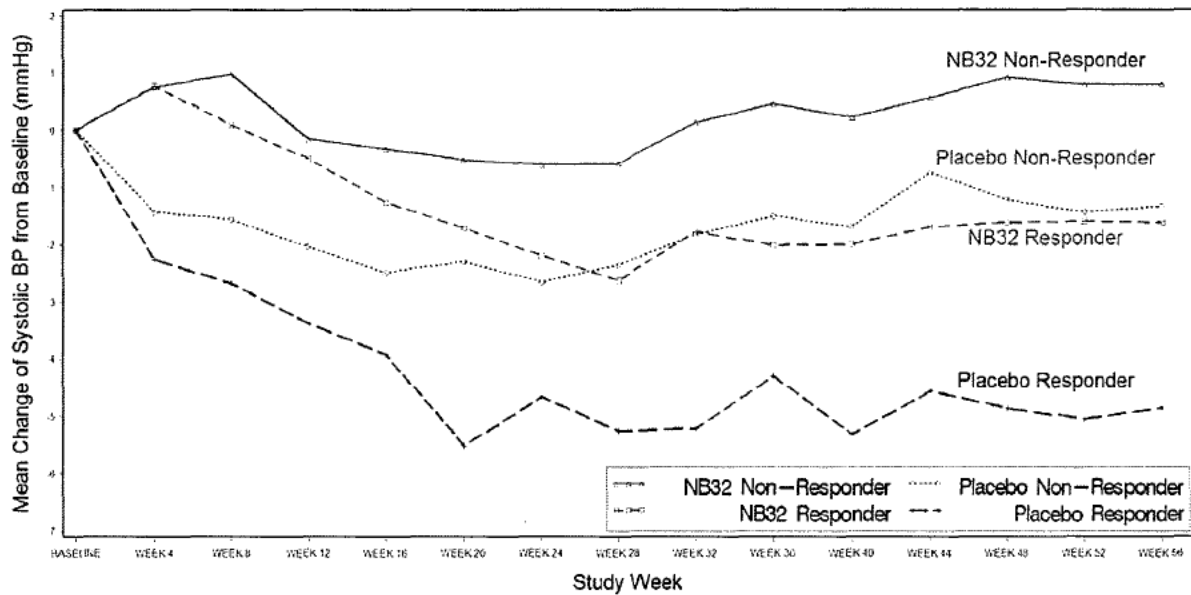
Enclosure:
Addendum

Addendum

Mean Weight Change at One Year for Various Obesity Drugs

	Active mean weight change at 1 year	Placebo mean weight change at 1 year	Data Source
Orlistat 120 mg TID	-6.1 kg	-2.6 kg	Xenical prescribing information
Sibutramine 15 mg QD	-6.4 kg	-1.6 kg	Meridia prescribing information
Qnexa (phentermine/topiramate) 15/92 mg QD	-11.4 kg	-1.9 kg	NDA 022580, FDA Briefing Package, EMDAC meeting, July 15, 2010
Lorcaserin 10 mg BID	-5.8 kg	-2.5 kg	NDA 022529, ISE Table 13
NB32 (naltrexone 32 mg /bupropion 360 mg) QD NB-301 (No DM)	-6.1 kg	-1.4 kg	Greenway FL, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. www.thelancet.com Published online 30 July 2010.

**Change of Systolic Blood Pressure by Treatment Response Group (Completers
Population)**



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/s/

CURTIS J ROSEBRAUGH
07/07/2011

6-16-11



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 200063

ACKNOWLEDGE DISPUTE APPEAL

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Senior Vice President, Global Regulatory Affairs
3344 North Torrey Pines Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone hydrochloride and bupropion hydrochloride extended-release tablets.

We acknowledge receipt on June 8, 2011, of your June 8, 2011, request for formal dispute resolution concerning the pre-approval requirement, cited in our January 31, 2011, complete response letter, for a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile.

We note that your request for a meeting with the appellate officer prior to a decision on this appeal, included in your June 8 submission, was withdrawn in your submission dated June 14, 2011.

Your appeal has been forwarded for review to Dr. Curtis Rosebraugh, Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research, and a response will be provided by July 8, 2011. We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301) 796-1282 or email me at leah.ripper@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Leah W. Ripper
Associate Director for Regulatory Affairs
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

LEAH W RIPPER
06/16/2011

Meeting Minutes
End of Review
May 25, 2011

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Review

Meeting Date and Time: May 26, 2011 at 3:00 pm to 4:30 pm
Meeting Location: FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, Maryland, 20993

Application Number: NDA 200063
Product Name: CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended Release tablets, 8mg/90mg
Indication: Treatment of obesity and weight management, including weight loss and maintenance of weight loss
Sponsor/Applicant Name: Orexigen Therapeutics

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Meghna M. Jairath, Pharm.D.

CDER ATTENDEES:

Office of Drug Evaluation II (ODE II)

Curtis Rosebraugh, MD, ODE Director

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, MD, Division Director

Meghna M. Jairath, Pharm.D., Regulatory Project Manager

Enid Galliers, Chief, Project Management Staff

Eric Colman, MD, Deputy Director

Eileen Craig, MD, Primary reviewer

Mary Roberts, MD, Medical reviewer

Patricia Brundage, Ph.D., Pharmacology/Toxicology reviewer

Division of Biometrics II (DB II), Office of Biostatistics

Janice Derr, Ph.D., Biometric reviewer

Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)

Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics VII (DB VII), Office of Biostatistics

Xiao Ding, Ph.D., Biometrics Reviewer

Mat Soukup, Ph.D., Biometrics Team Leader

Aloka Chakravarty, Ph.D., Division Director

Meeting Minutes
End of Review
May 25, 2011

SPONSOR ATTENDEES:

Orexigen Therapeutics, Inc.

Colleen Burns, PhD, Director, Biostatistics
Shawn Flanagan, PhD, Sr. Director, Clinical Pharmacology
Teri Johnson, RAC, Director, Regulatory Affairs & Development Strategic Planning
Preston Klassen, MD, Head of Global Contrace Program & Sr. VP of Product Development,
Michael Narachi, President and Chief Executive Officer
Dawn Viveash, MD, Sr. Vice President, Regulatory Affairs
Heather Turner, Esq., Senior Vice President, General Council & Secretary

Takeda Global Research & Development Center, Inc.

Lawrence Roebel, PhD, Sr. Director, Regulatory Affairs
Thomas Strack, MD, Vice President, Clinical Science

Outside consultants

[REDACTED] (b) (4)

Josephine Torrente, Attorney at Law

1.0 BACKGROUND

NDA 200063 was submitted by Orexigen as a 505(b)(2) combination for fixed dose product: Contrave [naltrexone HCl and bupropion extended release] tablets (8 mg/90 mg) for the treatment of obesity and weight management, including weight loss and maintenance of weight loss. Orexigen claims both products interact in the central nervous system to decrease food intake and increase energy expenditure, resulting in synergistic and sustainable weight loss.

FDA issued a complete response on January 31, 2011, stating that before Orexigen's application could be approved, they must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile. On March 9, 2011 Orexigen submitted a request for an end of review (EOR) meeting. The meeting was granted and scheduled for May 17, 2011 then rescheduled for May 26, 2011. Prior to the meeting, on May 25, 2011, FDA sent its preliminary comments to Orexigen via email.

Repeated below in regular text are Orexigen's question followed by FDA's preliminary responses written in **bold** text. The meeting discussion is highlighted in *italics*.

2. DISCUSSION

2.1. Clinical

Orexigen Question 1: Does the Division agree in principle with the following specific aspects of the proposed CV outcomes trial as detailed in the protocol synopsis:

a. Study design and schema?

FDA Preliminary Response: We do not agree with some of the major elements of your proposed cardiovascular safety trial. We would consider approval of Contrave based on interim data from a cardiovascular safety trial that incorporated and satisfied the below recommendations and criteria. Additional information regarding the below criteria will be discussed at the face-to-face meeting. Please be aware that we may need to take your application to a second advisory committee prior to considering approval based on interim or final data from a cardiovascular safety trial.

- We recommend that the population enrolled have an estimated annual placebo MACE rate of at least ~ 1.0 to 1.5%. This would necessitate enrolling some patients with a history of cardiovascular events and known risk factors, such as diabetes of substantial duration.

Meeting Discussion: Orexigen agreed to include some "higher-risk" subjects in the trial. See below.

- **The interim analysis must be done after > 50% of planned events have accrued and a reasonable portion of study participants have been treated for one year or more.**

Meeting Discussion: See below

- **The point estimate of the hazard ratio for MACE at the interim analysis must be close to or below unity with an upper bound of the 95% confidence interval that rules out 10 excess MACEs per 1000 person-years.**

Meeting Discussion: See below

- **The point estimate of the hazard ratio at the final analysis should be close to or below unity with an upper bound of the 95% confidence interval that rules out approximately 7 excess MACE per 1000 subject-years.**

Meeting Discussion: See below

- **The interim and final results of the primary outcome analysis should meet the above criteria for both the ITT and Per-Protocol populations (as defined below).**

Meeting Discussion: See below

- **The trial does not generate any new noncardiovascular safety signals that would alter Contrave's current benefit-risk profile.**
- **We request that you provide details regarding your proposed web-based MACE data collection system.**

Meeting Discussion: Orexigen did not provide this information during the meeting.

b. Definition of the primary MACE endpoint?

FDA Preliminary Response: We agree with your definition of MACE: CV death, nonfatal MI, and nonfatal stroke.

Meeting Discussion: None

c. Approach to data collection, including handling of MACE endpoints, blood pressure/heart rate data, and proposed efficacy measures?

FDA Preliminary Response: A treatment-emergent adverse event should be defined as an adverse event that has a start date on or after the first dose of study drug and up to 30 days after the last dose date of study drug. In addition:

- **Routine safety data collection should include all deaths, all AEs leading to discontinuation and all serious adverse events (SAE)s (not just SAEs of interest).**
- **Please provide details on how the blood pressure and pulse data will be collected**

Meeting Discussion: Orexigen did not provide details on the blood pressure or pulse data during the meeting.

d. Study populations (ITT and per protocol) and amount of excess risk to exclude at the preapproval and postapproval analyses?

FDA Preliminary Response: Refer to 1a comments.

Please confirm that in the ITT population all subjects who enter the trial will remain in the study until scheduled completion and will regularly provide information on body weight and primary safety outcome events even if they discontinue study drug (active or placebo). It will be important to encourage this in the consent form and other patient-directed materials.

Please confirm that in the Per Protocol population subjects are censored 30 days after discontinuation of study drug.

Meeting Discussion:

FDA: We anticipate that next year a general Advisory Committee meeting will be held to obtain feedback on the clinical development of drugs indicated to treat obesity. Some of the issues that may be discussed are whether all obesity drugs will require a cardiovascular (CV) outcomes trial vs. only obesity drugs with a CV signal and whether the trials should be designed as non-inferiority vs. superiority trials. If non-inferiority, we would anticipate a discussion of an acceptable point estimate and upper bound of the confidence interval for the hazard ratio.

The trial guidelines that we sent you are a reflection of the SCOUT trial and the number of excess events that led to sibutramine being withdrawn from the market. We acknowledge that the upper bound of the confidence interval and the point estimate of the hazard ratio are somewhat incongruent. Sibutramine was removed from the market due in large measure because the results of SCOUT indicated that the drug was associated with 3-4 excess major cardiovascular events per 1000 person years (HR 1.16), with an upper bound of the 95% CI consistent with ~ 7 excess events per 1000 person years (in the ITT population). The point estimate of the hazard ratio and the upper bound of the 95% CI were associated with ~ 5-6 and 9-10 excess events, respectively, in the per protocol or on-drug population. These numbers informed our recommendations regarding acceptable upper bounds at interim and final analyses of your proposed CV safety trial. We also reiterated our belief that the point estimate of risk at the interim and final analysis would need to be near unity.

We believe that for the Contrave CV trial, the point estimate of the hazard ratio should remain stable from the interim analysis to the final analysis while the width of the confidence interval should narrow.

Orexigen commented that if the point estimate is near unity, with adequate power, that the trial may be infeasible. Orexigen also had questions on the implications of a general broad advisory committee meeting and how this may impact the Contrave CV trial.

FDA commented that, at this point in time, we cannot give you an absolute cut-off for the hazard ratio point estimate but it should be near unity as sibutramine was withdrawn with a point estimate of 1.16--this is approximately 3-4 excess MACE events per 1000 subject-years. We acknowledge that it may be difficult to proceed with the trial as proposed with 90% power and that <90% power for the trial could be considered.

Orexigen did not feel they could proceed with a trial with less than 90% power.

FDA asked Orexigen if they had thought about doing a superiority trial. Orexigen responded that there was evidence of benefit based on the modeling studies that they had submitted but they did not want to pursue a superiority trial.

Orexigen commented that they proposed enrolling a patient population with an estimated annual placebo MACE rate of (b)(4)% as this will more accurately reflect the patients who will use the drug in the marketplace. Increasing the estimated MACE rate to 1.0 or 1.5% moves the patient population outside the target range and they estimate that this represents <10% of the population who will use the drug. Furthermore, enrolling a higher MACE rate will delay enrollment and the trial may need to move from a US trial to a more global trial to enroll this higher event rate.

The FDA commented that we often enroll subjects at a higher CV risk in order to fully evaluate the drug. If you do a study in a relatively healthy population, what is the risk if few events are captured? It is preferable to do the study in a higher risk population so at least you can confirm the degree of CV risk. Thus, the proposed study population, with an annual background MACE rate of (b)(4)%, does not include enough subjects at increased cardiovascular risk to adequately make an assessment of the effect of Contrave on cardiovascular risk.

Orexigen asked what other benefits would be compelling to the FDA. FDA responded that HbA1c, sleep apnea, arthritis outcomes, and quality of life from a validated scale could be considered but this would need to be discussed further with the divisions that evaluate these outcomes.

Orexigen asked if the Contrave Risk Engine that was previously submitted was compelling that Contrave treatment would not be expected to incur long-term CV risk. FDA replied that the Risk Engine was not particularly informative and would not replace the need for, at a minimum, reassuring interim data from a CV outcomes trial.

Orexigen asked about the interim analysis after at least 50% of events have accrued. Orexigen commented that the Diabetes Guidance allows for an interim analysis after ~ 25% of accrued events. FDA responded that the diabetes trials have many more events and the SCOUT trial has changed the landscape for obesity drugs and CV outcome assessments.

Orexigen asked about both the intent-to-treat (ITT) and per-protocol (PP) populations meeting the criteria for the interim and final results of the primary outcome analysis. FDA asked what the estimate is for subjects that will be off-study drug by the end of the trial. Orexigen estimated that 50-60% of subjects will be on active treatment at one year and that 36-38% of subjects will be on active treatment by the end of the trial.

Orexigen asked if they could power the study for the ITT population as the primary analysis population and the PP population would need to be consistent with the ITT population. FDA responded that this would be acceptable.

In summary:

- *At this time, SCOUT has established a benchmark for an unacceptable level of excess major cardiovascular events for an obesity drug with sympathomimetic properties.*
- *A general advisory committee meeting on CV outcomes trials for drugs indicated to treat obesity will be planned for 2012.*
- *An annual MACE of (b) (4)% in the control group might lead to a false sense of security and is not informative data. FDA will need to see an adequate number of CV events in order to evaluate the benefit-to-risk profile of Contrave.*
- *Efficacy thresholds in the 2007 Guidance should be accompanied by expected biomarker benefit—for Contrave, the fact that blood pressure and pulse did not track with the other benefits is concerning.*
- *The interim analysis for approval should be conducted after observing 50% or more of the total events—this is necessary due to the lower number of events and a reluctance to make an approval decision without sufficient data.*
- *The study can be powered for the ITT population but the PP results need to be consistent and not divergent from the ITT results; thus powering for only the ITT population may result in an underpowered study for comparisons using the PP population.*

Orexigen added that it is considering the appeal process for the Complete Response letter for Contrave.

Orexigen Question 2. If an interim analysis is acceptable to support approval, will the Division consider the remainder of the study to be a 505(o)(3) postmarketing requirement?

FDA Preliminary Response: Yes

Meeting Discussion: None.

Orexigen Question 3: Assuming key elements of the study design are agreed to at the End of

Review conference, Orexigen plans to prepare and submit a full draft protocol shortly thereafter. It is anticipated that the full statistical analysis plan (SAP) will not be finalized until after the study is initiated. Can the Division provide guidance regarding the timing of their review of a draft full protocol, as well as the preferred format for agreeing upon the protocol elements prior to finalization and study start?

FDA Preliminary Response: Deferred pending outcome of the EOR meeting.

Meeting Discussion: None.

Orexigen Question 4: The proposed CV outcomes trial includes a rigorous behavioral modification program for both treatment groups. As a result, the placebo treatment group in effect constitutes an active treatment arm rather than a more traditional (inactive) placebo comparator. Therefore, subjects treated with placebo are expected to experience significant weight loss similar to what was observed in Phase 3 Study NB-302. Although the results of the CV outcomes trial should be consistent with the range of results seen in the Phase 3 program overall, taken alone they may not meet the weight loss criteria outlined in the FDA guidance given the active comparator arm. Does the Division agree that the weight loss and associated cardiometabolic improvements demonstrated across the Phase 3 development program support product approval, providing that an agreed upon level of cardiovascular risk has been ruled out with the cardiovascular outcomes trial?

FDA Preliminary Response: We agree that the data submitted in the NDA satisfy the categorical weight loss efficacy criterion, as described in the 2007 draft guidance for weight management products. If however, data from the CV safety trial indicated a significant loss of weight-loss efficacy in Contrave versus placebo-treated subjects with treatment beyond one year, we may factor this information into the overall benefit-risk assessment of Contrave.

Meeting Discussion: None.

Orexigen Question 4 from the end of review meeting request dated March 9, 2011, is renumbered to “**Sponsor Question 5**” and is repeated below in regular text, FDA’s preliminary comment follow in **bold**.

Orexigen Question 5: Would limiting use of Contrave to patients at the lowest inherent CV risk, together with a commitment to complete a post approval CV outcomes trial as a means of potential long-term risk, alter the Division’s view of the approvability of Contrave with the data currently available?

FDA Preliminary Response: We would not consider approving Contrave for any population of patients without, at a minimum, reassuring interim data from a CV safety study.

Meeting Discussion: None.

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/s/

MEGHNA M JAIRATH
06/27/2011

3-30-11



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200063

MEETING REQUEST GRANTED

Orexigen Therapeutics, Inc.
Attention: Dawn Viveash, M.D.
Sr. VP, Global Regulatory Affairs
3344 North Torrey Pines Rd., Suite 200
La Jolla, CA 92037

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CONTRAVE (naltrexone hydrochloride/bupropion hydrochloride) Extended Release tablets, 8mg/90mg.

We also refer to your March 9, 2011, correspondence requesting an End of Review conference to discuss items listed in the complete response letter, dated January 31, 2011. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: May 17, 2011
Time: 1:00 pm to 2:30 pm
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

CDER participants:

Office of Drug Evaluation II (ODE II)

Curtis Rosebraugh, MD, ODE Director

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, MD, Division Director
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Enid Galliers, Chief, Project Management Staff
Eric Colman, MD, Deputy Director
Eileen Craig, MD, Primary reviewer
Todd Bourcier, Ph.D., Pharmacology/Toxicology Team Leader
Patricia Brundage, Ph.D., Pharmacology/Toxicology reviewer

Amy Egan, MD, Deputy Division Director for Safety
John Bishai, Ph.D., Safety Regulatory Project Manager

Division of Biometrics II (DB II), Office of Biostatistics

Jon (Todd) Sahlroot, Ph.D., Deputy Division Director and Statistics Team Leader
Janice Derr, Ph.D., Biometric reviewer

**Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP),
Office of Translational Sciences (OTS)**

Sally Choe, Ph.D., Team Leader
Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer

Division of Biometrics VII (DB VII), Office of Biostatistics

Xiao Ding, Ph.D., Biometrics Reviewer
Mat Soukup, Ph.D., Biometrics Team Leader

**Division of New Drug Assessment III, Office of New Drug Quality Assessment (ONDQA),
Office of Pharmaceutical Sciences (OPS)**

Patrick Marroum, Ph.D., Biopharmaceutics Supervisor
Tapash Gosh, Ph.D., Biopharmaceutics reviewer

Study Endpoints and Labeling Development (SEALD)

Elektra J. Papadopoulos, MD, MPH, Study Endpoints Reviewer
Elisabeth Piauxt-Louis, Study Endpoints Reviewer

Office of Surveillance and Epidemiology

Margarita Tossa, M.S., Safety Regulatory Project Manager
Suzanne Berkman Robottom, PharmD., Risk Management Team Leader, DRISK (Division of Risk Management)
Joyce Weaver, Pharm.D., BCPS, Senior Drug Risk Management Analyst, DRISK
Lanh Green, PharmD, MPH, Team Leader, Division of Pharmacovigilance I (DPV)
Selena Ready, PharmD., Safety Evaluator, DPV I

Good Clinical Practice Branch II, Division of Scientific Investigations, Office of Compliance

Sharon Gershon, Pharm.D., Captain, U.S. Public Health Service

Pediatric and Maternal Health Staff, Office of New Drugs

Mildred Wright, RN, MSN, Regulatory Health Project Manger

Please e-mail me any updates to your attendees at meghna.jairath@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined

as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Meghna M. Jairath, (301) 796-4267; Penya Littleton 301-796-2290.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 25 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by April 18, 2011, we may cancel or reschedule the meeting.

Submit the 25 desk copies to the following address:

If sending via USPS, please send to:

Meghna M. Jairath, Pharm.D.
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 3387
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS
(e.g., UPS, DHL), please send to:

Meghna M. Jairath, Pharm.D.
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 3387
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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

/s/

MEGHNA M JAIRATH
03/30/2011