

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200063Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	10 September 2014
From	James P. Smith, MD, MS
Through	Jean-Marc Guettier, MD
Subject	Summary Review for Regulatory Action
NDA#	200063
Applicant	Orexigen Therapeutics, Inc.
Date of Submission	10 December 2013
PDUFA Goal Date	11 September 2014
Proprietary Name ; Established (USAN) names	CONTRAVE ; naltrexone hydrochloride/bupropion hydrochloride extended-release tablets
Dosage forms ; Strength	Fixed-dose combination tablets of 8 mg/90 mg
Proposed Indication	Chronic weight management
Recommended:	Approve

Material Reviewed/Consulted		
Medical Officer Review	22 Aug 2014	Eileen Craig, MD
Statistical Review – Efficacy	14 May 2014	Lee Ping Pian, PhD
Secondary Statistical Review Memo	08 Sep 2014	Mark Rothmann, PhD
Statistical Review – Safety	12 May 2014	Janelle K. Charles, PhD
Clinical Pharmacology Review	23 May 2014	Manoj Khurana, PhD
CMC Review	02 Jun 2014	Xavier Ysern, PhD
Biopharmaceutics Review	05 May 2014	John Duan, PhD
Pharmacology/Toxicology Review	21 May 2014	Patricia Brundage, PhD
Clinical Inspection Summary/OSI	15 May 2014	Cynthia F. Kleppinger, MD
DRISK REMS Review	05 May 2014	Joyce Weaver, PharmD
OSE/DMEPA Labeling Consult	11 Mar 2014	Mishale Mistry, PharmD, MPH
OSE/DMEPA Proprietary Name Review	01 Apr 2014	Sarah K. Vee, PharmD
DMPP/OPDP Patient Labeling Review	14 May 2014	Shawna Hutchins, MPH, BSN (DMPP) & Kendra Y. Jones (OPDP)

CMC: Chemistry, Manufacturing, and Controls; OSI: Office of Scientific Investigations; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion; DMPP: Division of Medical Policy Programs

1. INTRODUCTION

This is the second review cycle for Contrave. This memorandum summarizes the principal review disciplines' evaluations of the data submitted during this review cycle, which focused predominantly on the assessment of the cardiovascular (CV) risk of Contrave. As discussed in this memorandum, a challenging aspect of this review arose when the review team became aware that the sponsor disseminated unblinded interim data from the ongoing cardiovascular outcomes trial, which was designed to characterize the CV risk of Contrave, far beyond the intended core group that the Agency expected to be involved in the regulatory submission of this application. As discussed in this memorandum, this unanticipated extent of data sharing

has impacted the Agency's approach to the post-marketing requirement to further characterize the CV safety of Contrave.

This memorandum does not provide a detailed summary of the data evaluated during the first review cycle for Contrave (e.g., the phase 3 program, efficacy/safety as it relates to weight loss, etc.). For that, I refer to Dr. Eric Colman's summary review, signed 31 January 2011.

I am not aware of any disagreements between primary reviewers regarding the approvability of this application; all have recommended approval.

2. BACKGROUND

Contrave is a fixed-dose combination of naltrexone HCl and bupropion HCl, both of which are currently approved in the United States: naltrexone for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids, and bupropion for the treatment of major depressive disorder and as an aid to smoking cessation treatment. The applicant, Orexigen Therapeutics, Inc., originally submitted a new drug application (NDA 200063) for Contrave on 31 March 2010, proposing that the drug "...is indicated for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification."¹

A complete response letter (CRL) issued 31 January 2011, citing statistically significantly higher mean systolic and diastolic blood pressure and heart rate among naltrexone/bupropion-treated subjects compared with placebo-treated subjects. In addition, more adverse events related to hypertension were observed in the naltrexone/bupropion groups, particularly among subjects with type 2 diabetes. Collectively, this raised concern about the cardiovascular safety profile of naltrexone/bupropion when used long-term in a population of overweight and obese individuals. The letter stated, "Therefore, before your application can be approved, you 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."²

Subsequent to an end-of-review meeting in which the Division discussed design elements of the required CVOT,³ the applicant disputed the Division's action by submitting formal dispute resolution requests (FDRRs) to the Office of Drug Evaluation II (ODEII), the Office of New Drugs (OND), and the Center for Drug Evaluation and Research (CDER). The specific arguments presented within each dispute are beyond the scope of this memo. Although each of these FDRRs was denied,⁴ the response from OND outlined features of the design and analysis for a trial that could satisfy the Division's requirement of establishing cardiovascular safety. The letter supported the conduct of an interim analysis to support approval with a

¹ Proposed labeling submitted 31 March 2010, NDA 200063 (Module 1.1.4.1.3).

² Complete response letter, NDA 200063, 31 January 2011.

³ End-of-review meeting minutes, NDA 200063, 27 June 2011.

⁴ FDRR denial letters dated 07 July 2011 (ODEII; Dr. Curtis Rosebraugh), 15 September 2011 (OND; Dr. John Jenkins), and 15 October 2012 (CDER; Dr. Douglas Throckmorton).

final analysis to occur after approval; i.e., a paradigm similar to that described in the December 2008 Guidance for Industry titled, *"Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes."*⁵ For a population with a background risk for major adverse cardiovascular events (MACE) of 1.0-1.5%, which was also recommended in the letter, the interim analysis was to exclude a hazard ratio (HR) of 2.0 (upper bound of the 95% confidence interval [CI]) and the final analysis was to exclude a HR of 1.4. The letter stated that ruling out a HR of 2.0 at the interim analysis would require at least 87 MACE, or approximately 25% of the planned events for the trial. Furthermore, OND did not object to the firm's proposal to stop drug therapy in patients who did not demonstrate some pre-specified level of weight loss, as long as all continued to be followed for MACE. The intent-to-treat (ITT) analysis would be considered primary, although a per-protocol analysis would also be reviewed.

The protocol for the required cardiovascular outcomes trial (CVOT), also referred to as the LIGHT trial or NB-CVOT, was reviewed and agreed upon under a Special Protocol Assessment.⁶ The protocol incorporated the design and analysis features outlined in the FDRR denial letter from OND. The first subject was enrolled 01 June 2012, and the cut-off date for the first interim analysis, which forms the basis for this NDA resubmission, was 06 November 2013. The Data Monitoring Committee (DMC) met on 23 November 2013 to review the interim results and informed Orexigen that the pre-specified monitoring boundary had been met. Based on the interim results from NB-CVOT, the NDA was resubmitted on 11 December 2013, with a follow-up submission on 07 February 2014 by previous agreement.

3. CMC

Although not listed as an approvability issue, the CRL noted that the proposed dissolution specifications were not acceptable. Furthermore, the evaluation of the effect of alcohol (ethanol) on the *in vitro* dissolution of bupropion hydrochloride or naltrexone hydrochloride was deficient. Dr. Duan reviewed the applicant's responses in this submission and found them acceptable. Dr. Ysern noted that besides dissolution specification, there were no CMC-related changes since 17 December 2010. I agree that there are no outstanding CMC-related issues that would preclude approval.

Facilities Review/Inspection

On 29 May 2014, the Office of Compliance issued an "Acceptable" overall recommendation for this NDA. There are no pending cGMP inspection issues.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No nonclinical issues were cited in the CRL; pharm/tox supports approval. Naltrexone and bupropion, as well as hydroxybupropion (the major active metabolite of bupropion in humans), possess CNS activity with the potential to cause adverse outcomes or irreversible

⁵ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>

⁶ Special Protocol Agreement letter, IND 68858, 03 February 2012.

effects on learning, memory, and behavioral development as a result of exposure during the pre-pubertal/post-pubertal period. Because of this, Dr. Brundage recommends, as a post-marketing requirement (PMR), a juvenile animal study with the combination of bupropion and naltrexone to assess behavior/motor activity, learning and memory, growth, sexual maturation, and mating/fertility prior to initiating pediatric safety and efficacy studies. I concur with this recommendation.

5. CLINICAL PHARMACOLOGY

Dr. Khurana's clinical pharmacology review provides updated thinking regarding some of the issues highlighted in his original review (dated 23 December 2010). Specifically, his review addresses (1) use in hepatic impairment, (2) use in renal impairment, and (3) an updated recommendation regarding an *in vivo* drug-drug interaction (DDI) study with an OCT2 substrate. Regarding use in the setting of hepatic or renal impairment, Dr. Khurana notes that the effects of these conditions on the PK of bupropion and naltrexone from Contrave are not fully understood; therefore, single-dose PK studies in these populations will be conducted as post-marketing requirements. Last, in the CRL, it was noted that an *in vivo* DDI study evaluating the impact of Contrave on an OCT2 substrate such as metformin hydrochloride would be required after approval; this study will also be a post-marketing requirement. The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 recommends approval. I agree that there are no outstanding issues related to clinical pharmacology that preclude approval.

6. CLINICAL & BIOSTATISTICS

NB-CVOT (LIGHT trial)

Trial Description & Summary of Interim Analysis

Details regarding the design, conduct, demographics and baseline characteristics, subject disposition, (interim) analyses of the primary endpoint (MACE⁷) and secondary endpoints, and analyses of the LIGHT safety database to date are thoroughly described in the reviews of Dr. Craig and Dr. Charles.

Briefly, the LIGHT trial is an ongoing multicenter, double-blind, 1:1 randomized, placebo-controlled, event-driven trial that includes subjects with overweight or obesity who are at increased risk of CV events. The trial is being conducted at 264 sites in the United States. After a screening period, subjects enter a 2-week double-blind lead-in period (one week Contrave 8 mg/90 mg once daily and one week matching placebo, in random order), followed by a double-blind treatment period of approximately 4 years. Contrave is titrated to a maximum daily dosage of 32 mg naltrexone SR/360 mg bupropion SR (split-dosing, twice daily) during the first 4 weeks of the treatment period. At Week 16, there is a planned evaluation of weight loss and blood pressure (BP) relative to baseline, and subjects are

⁷ Major adverse cardiovascular events, defined as the first occurrence of CV death, nonfatal MI, or nonfatal stroke.

discontinued from trial medication at this visit if they have not lost at least 2% of their body weight or they have consecutive, sustained increases in systolic or diastolic BP of ≥ 10 mmHg. Regardless of whether subjects discontinue from treatment or study procedures, they are to be contacted to assess for the occurrence of MACE unless they revoke consent for all further follow-up.

The agreed-upon primary analysis population is all randomized subjects who were dispensed medication. The primary analysis is time from randomization to first MACE, including all post-randomization events through the analyses cut-off date regardless of whether subjects discontinued treatment (“on-study” analysis). “On-treatment” analyses, which only included MACE that occurred while a subject was on treatment (or within 30 days of treatment discontinuation) were also conducted. All MACE included in the analyses were events adjudicated as such by an independent blinded committee that used standardized definitions.

Enrollment of the LIGHT trial, as originally designed, is complete. The primary analysis (ITT) population for this interim analysis comprised 4455 Contrave and 4450 placebo subjects. Distributions of demographic and CV risk factors were similar between treatment groups, with the majority of subjects being female (55%) or white (84%). The average age was 61 years and the average BMI was 37 kg/m², with 85% of subjects having type 2 diabetes and 32% having a history of CV disease.

As shown in Table 3 (p. 24) of Dr. Charles’s review, as of the interim analysis cut-off date, 62% of Contrave subjects and 73% of placebo subjects have discontinued treatment. These rates of treatment discontinuation are more consistent with the predicted rates at Year 3 as opposed to the observed ~1.5-year timepoint. The most common reason for treatment discontinuation in Contrave-treated subjects was adverse events primarily related to tolerability (e.g., nausea), and the most common reason for treatment discontinuation in placebo-treated subjects was not meeting the Week 16 weight-loss criterion. I note that the Week 16 BP criterion contributed to the decision to discontinue treatment in 3.5% of Contrave-treated subjects and 5.2% of placebo-treated subjects.

In addition, 29% of Contrave subjects and 32% of placebo subjects have discontinued the trial, although most continue to be followed for MACE (e.g., via contact with their physician). The percentages of subjects who have been completely lost to follow-up for MACE events are 4.9% and 4.7% for the Contrave and placebo groups, respectively, leaving approximately 95% of the ITT population available for MACE analyses. Dr. Charles notes that the *a priori* estimate of the annual rate of trial discontinuation was 1.2%, yet the loss to follow-up rate is approximately 5% at approximately 1.5 years; this could potentially impact the ability of the trial to attain the expected number of events by the estimated maximum duration of 4 years.

The first planned interim analysis, which forms the basis for the current resubmission, yields an estimated HR for MACE with an upper bound of the 95% CI that is less than 2.0 in the on-study analysis. An on-treatment analysis using the ITT population also excluded the 2.0 risk margin.

Dr. Charles conducted sensitivity analyses to evaluate the possibility of a biased result due to informative censoring (e.g., if censored subjects who have SAEs that could have later developed into MACE events were discontinued from follow-up shortly after the SAE occurred). She notes that these sensitivity analyses yielded results consistent with the on-study and on-treatment analyses with respect to testing the 2.0 HR risk margin. Analyses of an expanded MACE (MACE + hospitalization for unstable angina) composite, individual MACE components, and all-cause mortality were also performed; none produced results that would preclude approval. Both Dr. Craig and Dr. Charles conclude that this interim analysis of the LIGHT trial has demonstrated that the upper bound of the 95% CI for the estimated HR (Contrave vs. placebo) for MACE is <2.0. I concur with their assessment.

Concerns Regarding Data Sharing After Interim Analysis

Maintaining confidentiality of interim results from a trial is essential to maintain integrity and credibility of the ongoing trial. In general, knowledge of interim results by those involved in the conduct of the trial or the trial's participants could have many adverse effects, such as slowing recruitment, promoting dropouts or cross-ins, introducing bias with regard to outcome assessment or safety-related events, and amending the design of the trial itself based on interim knowledge. These potential consequences of leaking interim results have been well articulated in the literature (see related published work of Dr. Thomas Fleming for examples⁸). As the 2006 FDA Guidance for Clinical Trial Sponsors – *Establishment and Operation of Clinical Trial Data Monitoring Committees* states, "Knowledge of unblinded interim comparisons from a clinical trial is generally not necessary for those conducting or sponsoring the trial; such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of the analyses."⁹

The review team requested that Orexigen submit the DMC meeting minutes corresponding to discussion of the November 2013 interim analysis as well as the Data Access Plan (DAP) mentioned in the DMC charter; the DAP was to be created to ensure that only the unblinded team members would have access to the unblinded interim NB-CVOT data. These documents were provided as part of an official submission on 07 February 2014. Included in the minutes of the open portion of the 23 November 2013 DMC meeting, the team took note of the following:

"There was extensive discussion regarding the current version of the Data Access Plan that addresses criteria for access to unblinded data from the interim analysis of the trial. All agreed on the general principle, as stated in the DMC Charter, that access to confidential information on efficacy and safety will be limited to the 'core group of individuals essential to the facilitation of the resubmission,' and that access to these interim data, including the hazard ratio estimate and confidence interval for the primary endpoint, should be limited to the DMC, the regulatory authorities, and the 'unblinded team.' **It further was discussed that business interests do not provide a sufficient justification for gaining access to confidential information on efficacy or safety. It was agreed that the Data Access Plan will need to be**

⁸ Examples include Demets DL and Fleming TR. The independent statistician for data monitoring committees. *Statist Med* 2004; 23:1513-1517; and Fleming TR, et al. Maintaining confidentiality of interim data to enhance trial integrity and credibility. *Clinical Trials* 2008; 5:157-167.

⁹ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>

substantively revised and that the revised agreement will be valid through the entirety of the trial” (emphasis added).

The submitted DAP (version 2, dated 03 February 2014) states that the unblinded team is limited to those individuals needed to facilitate or manage global regulatory submissions. Recognizing that the DMC minutes suggested that a suboptimal DAP might have been in place at the time of the interim analysis, the review team requested a list of individuals, excluding DMC members, who had knowledge of the interim results or access to unblinded interim data. On 16 April 2014, the applicant provided a list of more than 100 individuals who had knowledge of the interim results or access to unblinded interim data.¹⁰ Dr. Charles notes that it is particularly concerning that members of Orexigen’s Board of Directors, who have financial interest in the outcome of the trial, were also provided full access to unblinded data. Dr. Craig notes that others include the Orexigen CEO, investment bankers, and several representatives from Takeda Pharmaceuticals (including Corporate Communications, Chief Commercial Officer, and Head of Global Marketing). Furthermore, the list of unblinded individuals is noted not to include the names of potential (b) (4) who have also obtained knowledge of the unblinded interim results because “we [Orexigen] have entered into confidentiality agreements with each of the potential (b) (4)

As described above, unblinded interim results are expected to be shared only with the DMC and a select set of personnel, essential for a regulatory submission, separated by an appropriate firewall. This core group is also expected to be functionally independent of the operational aspects of the trial; in this case, with more than 100 individuals having access to interim results, including those with business interests in the trial, the review team has serious concern about the ability to maintain the integrity of the ongoing trial such that the final results could, on their own, reliably assess the HR risk margin of 1.4. Furthermore, Dr. Charles notes that “there is no direct way to measure or assess the impacts of this level of unblinding on the conduct of the trial and its influence on the interpretability of data generated after the blind was broken.”

Because the concerns regarding dissemination of unblinded data arose after the interim analysis, there is no debate among the review team that the upper bound of the 95% CI for MACE is less than 2.0; therefore, the interim data can be used to rule out the agreed-upon pre-approval risk margin. Dr. Charles concludes in her review, however, that for serious risks (i.e., CV risk) that warrant assessment through a randomized clinical trial, “it is imperative that the trial be conducted to the highest of scientific standards as there is typically only a single opportunity to reliably characterize the risk.... However, the Applicant has taken actions that have the potential to compromise the integrity of the LIGHT trial raising concerns about the ability to rely on data generated after the blind was broken to rule out the 1.4 risk margin. This in turn raises questions about the suitability of the LIGHT trial to achieve its

¹⁰ Provided via email on 16 April 2014 with subsequent official submission to NDA on 30 May 2014. The extent of information included in this submission was determined to be a major amendment to the application, extending the goal date by three months to provide time for a full review of the submission and its potential implications.

ultimate objective in characterizing the CV risk of CONTRAVE. Due to these concerns one can postulate that the LIGHT trial is not being conducted to the highest of scientific standards. As such, we recommend a new cardiovascular outcome trial that is held to the highest of scientific standards be initiated with the objective of ruling out a relative CV risk of 1.4 " (pp. 36-37).

As discussed by Dr. Charles, even if concerns did not arise because of the extent of the dissemination of interim data, the high percentage of treatment discontinuations calls into question the ability to interpret the final results should the LIGHT trial continue to completion, given that the majority of events may be observed after subjects discontinued treatment. She estimated the total number of on-treatment events that may be expected at completion of the LIGHT trial in 2.5 years under three different scenarios; of the 378 total events expected at the conclusion of the trial, Dr. Charles estimates that 83 to 134 may occur on treatment, raising the possibility that results from the on-study analysis and on-treatment analysis may be divergent. In their 23 November 2013 meeting, the DMC raised similar concerns and recommended enrolling an additional cohort of subjects to achieve the required number of endpoints with a lower average duration of follow-up. To my knowledge, the applicant has not yet implemented this recommendation.

The extent of the applicant's sharing of the interim data became the subject of multiple internal meetings with senior management across the Center, as well as face-to-face meetings with the applicant on 04 June 2014 and 24 July 2014. There was consensus within the Agency that the number of individuals who had received knowledge of the interim results and/or access to patient-level data listings (which included treatment assignments) was far greater than the Agency considered "essential" to facilitate resubmission of the NDA. Ultimately, on 20 August 2014, the applicant was informed that the Agency had 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' MACE, cannot serve as the primary basis to exclude the possibility that Contrave increases the risk for MACE by 40% or more.¹¹ After much discussion, we are not confident that we would ultimately be able to detect or exclude the possibility that the applicant's activities may have biased the trial's results or otherwise compromised its integrity. Thus, the LIGHT trial will not satisfy a post-marketing requirement related to CV safety. However, despite this conclusion, the Agency strongly encouraged the applicant to continue the LIGHT trial since it may provide supportive evidence when the effects of Contrave on CV 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 LIGHT might provide complementary support. Furthermore, although difficult to predict at the present time, it is plausible that scientific questions may arise during the review of either trial such that the availability of data from a second trial, despite potential limitations, may be beneficial.

¹¹ General advice letter, Dr. Jean-Marc Guettier, NDA 200063, 20 August 2014.

The Agency will require 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.

Weight Loss in NB-CVOT

Although not the primary objective of NB-CVOT, Dr. Craig noted that in NB-CVOT, the proportion of subjects achieving $\geq 5\%$ weight loss from baseline to Week 52 was statistically significantly greater with Contrave than placebo (32.7% vs. 12.9%, $p < 0.0001$) in the ITT population. At Week 52, the least-squares mean percent change in body weight from baseline was -2.7% in the Contrave arm and +0.03% in the placebo arm, yielding a treatment difference of -2.8%. Only 45% of subjects had completed the Week 52 visit prior to the interim analysis cut-off date, however; therefore, the last observation taken at the time of the cut-off was carried forward to Week 52 for those subjects receiving medication who had not yet reached Week 52. Furthermore, as noted previously, subjects who had not lost at least 2% of body weight by Week 16 were discontinued from treatment; therefore, for several reasons, these data cannot be compared directly with the phase 3 weight-loss trials. Thus, I do not believe these interim data provide new information that substantively informs the efficacy of Contrave with respect to weight loss.

Weight-Loss Threshold at Week 16 for Continued Treatment

Dr. Pian used body weight data from week 52 in NB-CVOT to perform analyses to identify a weight loss threshold at an earlier week to predict the likelihood of weight loss $< 5\%$ at week 52. She noted that these analyses were limited, as there were no prospective plans to test various cutpoints of discontinuing therapy and there was no randomization to either continue or discontinue therapy. Although Dr. Pian recommended that a weight loss of $< 3\%$ at week 16 could be used to identify patients who are less likely to have $\geq 5\%$ weight loss at week 52, discussion of the data with the clinical team led Dr. Craig to recommend using the sponsor's previous proposal (labeling proposed in 2011) that if a patient has not exhibited at least 5% weight loss after four months of treatment (i.e., three months after reaching the maintenance dose if titrated according to the recommended schedule), the physician should consider discontinuation of Contrave. The statistical team did not disagree with this recommendation, and I concur.

7. NON-CARDIOVASCULAR SAFETY

Dr. Craig reviewed safety data from the interim analysis of NB-CVOT and qualitatively compared the safety profile observed in the safety database included in the original NDA

submission with that observed in NB-CVOT to date. I will summarize selected results from her evaluation of NB-CVOT here; refer to Dr. Craig's review for additional details.

As of the NB-CVOT interim analysis, the median durations of time on study medication for the Contrave and placebo groups were 18.6 weeks and 16.3 weeks, respectively. There were 39 deaths overall, and their distribution across the treatment groups did not raise concern. At least one nonfatal serious adverse event (SAE) was reported by 6.1% and 5.6% of subjects in the Contrave and placebo groups, respectively. More subjects had adverse events leading to discontinuation of study medication (AELDSMs) in the Contrave group than the placebo group (25.5% vs. 7.3%), primarily a result of AEs in the Gastrointestinal Disorders SOC (13.7% vs. 1.7%), Nervous System Disorders SOC (5.0% vs. 1.0%), Psychiatric Disorders SOC (2.8% vs. 0.9%), and General Disorders and Administrative Site Conditions SOC (1.6% vs. 0.4%). The events responsible for the majority of AELDSM among Contrave-treated subjects were nausea, constipation, vomiting, tremor, dizziness, and headache.

In her review, Dr. Craig addresses areas of particular safety interest, including blood pressure/pulse, cardiovascular events, psychiatric-related adverse events, neurologic/cognitive adverse events, the incidence of increases in serum creatinine, and liver-related safety. I have already addressed the interim analysis with respect to MACE above; additional serious CV-related safety concerns that would not have been captured by MACE were not identified.

In NB-CVOT, there were more psychiatric SAEs and AELDSMs in the Contrave arm than placebo (SAEs: 0.1% vs. <0.1%; AELDSM: 2.8% vs. 0.9%). SAEs in the Contrave arm included one each of the following preferred terms: anxiety, delirium, hallucination, major depression, and mental status changes. A single SAE of depression and a single SAE of suicide occurred in subjects treated with placebo. The most common psychiatric AELDSMs among Contrave-treated patients included insomnia, anxiety, hallucination, and nervousness.

Bupropion is contraindicated in patients with a seizure disorder, and the risk of seizure appears to be strongly associated with bupropion dose according to its prescribing information. In the phase 3 trials, 2 (0.08%) of 2545 of Contrave-treated patients, neither of which had a prior history of seizures, experienced a seizure compared with none in placebo-treated patients. In NB-CVOT, there was one SAE of seizure in the Contrave group and none in the placebo group; this subject had type 2 diabetes and chronic kidney disease, although the patient had a baseline eGFR of 92 mL/min. There was no clear alternative etiology of the event.

With regard to nervous system disorders, SAEs were similar between treatment groups in NB-CVOT (0.5% Contrave vs. 0.4% placebo). The incidence of AEs related to nervous system disorders leading to study drug discontinuation was higher for Contrave than placebo (5.0% vs. 1.0%), primarily resulting from events of tremor, dizziness, headache, dysgeusia, and disturbance in attention.

Renal and urinary disorder SAEs have been infrequent in NB-CVOT, occurring in 0.1% of Contrave-treated subjects and 0.3% of placebo-treated subjects. AELDSM of "blood creatinine increased" occurred in 3 Contrave-treated subjects and 1 placebo-treated subject.

In the phase 3 program, no subjects met criteria for Hy's law and the incidence of transaminase elevations was similar between treatment groups. In NB-CVOT, there was one Contrave-treated subject with an SAE of suspected drug-induced liver injury (DILI).¹² This was a 66-y/o man who was treated with Contrave for 40 days before study medication was interrupted as a result of nausea and vomiting and was subsequently discontinued as a result of DILI (verbatim term: possible drug-induced hepatitis). The patient was taking multiple concomitant medications. Three days after the last dose of Contrave, the subject had elevated hepatic transaminases (ALT 9.3xULN, AST 4.2xULN) and symptoms of hepatitis, accompanied by deterioration of pre-existing borderline renal impairment. The bilirubin was 1.1 mg/dL (ref range, 0.2-1.0). Hepatitis serologies were not performed. No stones or biliary duct dilatation were observed on ultrasound. The subject recovered, with hepatic transaminases and renal function returning to the normal range. Dr. Craig felt that causality assessment is confounded by the use of concomitant medications that have the potential to contribute to DILI, but a causal relationship to Contrave cannot be definitely excluded.

Taken together, Dr. Craig concludes that the safety profile observed in NB-CVOT to date is consistent with the known effects of the components of Contrave (naltrexone and bupropion), with no new safety signals observed in this trial compared with the phase 3 trials.

8. ADVISORY COMMITTEE MEETING

This resubmission was not discussed at an advisory committee meeting. The original Contrave application was discussed at an advisory committee on 07 December 2010 (with a vote of 13 vs. 7 in favor of the potential benefits of Contrave outweighing the potential risks).

9. PEDIATRICS

This application was discussed with the Pediatric Review Committee (PeRC) on 30 April 2014. The requirement for pediatric studies for ages 0 to 6 years (inclusive) will be waived because the necessary studies are impossible or highly impractical, since weight loss is not recommended in children < 2 years old and weight maintenance (not weight loss) is the clinical goal for obese children 2 to 6 years old. Deferred pediatric studies will include (1) a juvenile animal study, (2) a clinical pharmacology study followed by a 52-week efficacy/safety study in 12- to 17-year-old patients (inclusive), and (3) a clinical pharmacology study followed by a 52-week efficacy/safety study in 7- to 11-year-old patients (inclusive). The juvenile animal study should precede the efficacy/safety studies, and the adolescent efficacy/safety study should precede the efficacy/safety study in younger children.

¹² A second subject (61-y/o female) developed dyspnea on day 272 and had the incidental finding of cirrhosis on a CT scan performed as part of her evaluation. Her dyspnea was subsequently determined to be the result of hepatopulmonary syndrome.

10. OTHER RELEVANT REGULATORY ISSUES

Financial Disclosure

Dr. Craig noted that the applicant adequately disclosed financial interests/arrangements with clinical investigators (p. 36 of Clinical Review).

Clinical Inspections

Routine inspections of five domestic clinical sites as well as the contract research organization for the NB-CVOT trial were conducted. For three of the sites, the data were considered reliable based on the available information and support validity of data as reported by the sponsor under the NDA. Two site investigators and the contract research organization were each issued a Form 483 citing inspectional observations; classifications for each were Voluntary Action Indicated (VAI). Dr. Kleppinger concluded, however, that although regulatory violations were noted, they are unlikely to significantly impact primary safety and efficacy analyses. Thus, the overall data in support of this application may be considered reliable based on the available information.

Proprietary Name Review

The Division of Medication Error Prevention and Analysis and the Office of Prescription Drug Promotion concluded that the proposed proprietary name, Contrave, is acceptable from a safety and promotional perspective.

11. LABELING

Dr. Craig and Dr. Charles recommend that none of the findings of the pre-approval interim analyses of the LIGHT trial be included in labeling. In addition, because the CV safety of Contrave has not been confirmed with these interim data, they recommend inclusion of a Limitation of Use statement that the effect of Contrave on CV morbidity and mortality has not been established. I concur with their recommendation.

Contrave will have a boxed warning, similar to other bupropion products, for suicidality and for neuropsychiatric events.

Dr. Rothmann recommends that the sponsor's ITT analysis be used in labeling for providing the treatment effect of Contrave on weight. Although this was not the pre-specified analysis, Dr. Rothmann noted that the pre-specified analysis¹³ excluded 12-17% of subjects in the Contrave arm in the ITT population and 1.5-5% of subjects in the placebo arm in the ITT population; this was largely because of early discontinuations. Dr. Rothmann notes that part

¹³ The primary analysis population was the Full Analysis Set (FAS), defined as all subjects who were randomized, had a baseline body weight measurement, and at least one post-baseline body weight measurement on study drug. The primary analysis only considered body weight measurements while on study drug and used last-observation-carried-forward (LOCF) imputation.

of a therapy's effect is mediated through the ability to tolerate the therapy. He points out that, on average, subjects who discontinued Contrave and later had their weight measured at 56 weeks had little change in weight from baseline. He believes that missing data should be addressed in the most appropriate way to provide the most relevant estimate of the treatment difference/effect; therefore, in the case of Contrave, the recommendation of the Division of Biometrics 2 is to use the sponsor's ITT analysis for labeling related to the primary endpoint (change in weight). I note that this is similar to the analysis that is presented in labeling for Qsymia.

Contrave will have a Medication Guide for patients. The Division of Risk Management believes that this Medication Guide, dispensed outside of a REMS, is sufficient to mitigate the risks associated with Contrave. They do not recommend that a REMS be required for Contrave at this time. I concur with their recommendation.

12. DECISION/ACTION/RISK BENEFIT ASSESSMENT

Refer to Dr. Eric Colman's 31 January 2011 summary review for a discussion of the benefit/risk of Contrave that addresses issues other than CV risk. The only approval deficiency cited in the 31 January 2011 CRL was that the applicant must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk for MACE in overweight and obese subjects treated with Contrave does not adversely affect the drug's benefit-risk profile. As described previously, it was ultimately determined that the applicant would need to exclude a hazard ratio for MACE of 2.0 before approval and 1.4 after approval. Despite the serious concerns raised by the extent of the applicant's dissemination of interim results from the LIGHT trial, these activities occurred after the interim analysis; therefore, the interim data can be used to rule out the agreed-upon pre-approval risk margin and a new cardiovascular outcomes trial will be required to satisfy the post-marketing requirement related to further characterizing cardiovascular safety. No new safety signals were identified during the review of the interim results from the LIGHT trial that would alter the benefit/risk conclusion. Thus, this application can be approved.

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

09/10/2014

JEAN-MARC P GUETTIER

09/10/2014

I concur with Dr. Smith's detailed review of the main issues in this resubmission. I am in full agreement with his recommendations and his rationale for making these recommendations. I recommend approval of this application. Dr. Colman's 31 January 2011 and Dr. Smith's reviews serve as the summary basis for approval of this application.

Summary Review for Regulatory Action

Date	January 25, 2011
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	200063
Applicant Name	Orexigen Therapeutics, Inc.
Date of Submission	31 March 2010
PDUFA Goal Date	31 January 2011
Proprietary Name /Established Name	Naltrexone/Bupropion - Contrave
Dosage Forms / Strength	Fixed-dose combination - 32mg/360mg
Proposed Indication(s)	Weight Management
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Eileen Craig, MD
Statistical Review	Janice Derr, PhD (efficacy)/Xiao Ding, PhD (safety)
Pharmacology/Toxicology Review	Patricia Brundage, PhD
CMC/OBP Review	Xavier Ysern, PhD/Tapash Ghosh, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Manoj Khurana, PhD
DDMAC	NA
DSI	Sharon Gerson, PharmD/Bonita Chester
DMEPA	Richard Abate RPh/Denise Toyer PharmD
DRISK	Joyce Weaver, PharmD/Shawana Hutchins
Thorough QT Consult	Monica Fiszman, PhD
Controlled Substance Staff	Chad Ressig, PhD

OND=Office of New Drugs

CMC=Chemistry, Manufacturing, and Controls

OBP=Office of Biopharmaceutics

DDMAC=Division of Drug Marketing, Advertising and Communication

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK=Division of Risk Management

1. Introduction

This memorandum summarizes the conclusions and regulatory recommendations of the review disciplines assigned to this application. I am not aware of any significant disagreements within or between the review disciplines regarding final regulatory recommendations. This memo pays particular attention to cardiovascular safety.

2. Background

Orexigen Therapeutics is seeking approval of a fixed-dose combination of 32 mg naltrexone and 360 mg bupropion (hereafter NB32) for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, in 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).

Naltrexone, a mu-opioid receptor antagonist, was approved by FDA for opioid addiction in 1985 and alcohol dependence in 1995. The usual adult dose is 50 mg/day. Bupropion, a neuronal reuptake inhibitor of norepinephrine and dopamine, was approved by FDA for depression in 1985, smoking cessation in 1997, and seasonal affective disorder in 2006. The usual adult dose is 300 mg/day, with a maximum daily dose of 400 mg.

Based on elevations in serum transaminase levels in obese subjects treated with large doses of naltrexone, the approved labeling for naltrexone carries a boxed warning for potential hepatotoxicity. Based on a meta-analysis of anti-depressant medications, the labeling for bupropion includes a boxed warning for suicidality. Bupropion increases the risk for seizures in a dose-dependent manner. At 300 mg/day, the incidence of seizure is estimated to be 1/1000 and increases to 4/1000 at 400 mg/day.

Because bupropion can increase blood pressure and heart rate, at the End-of-Phase 2 meeting the Division raised the possibility that Orexigen might be required to conduct a cardiovascular outcomes trial with NB32.

3. CMC/OBP

According to Dr. Ysern there are no outstanding deficiencies. He recommends that the application be approved. Dr. Ghosh has several non-approvability recommendations that will be conveyed to the company in the Complete Response letter. I agree that there are no outstanding CMC or biopharmaceutics issues that would preclude approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

Dr. Brundage recommends approval of the NDA. I agree that there are no outstanding nonclinical pharmacology/toxicology issues that would preclude potential approval of this NDA.

5. Clinical Pharmacology

The clinical pharmacology reviewer concludes that the data submitted in support of the application are acceptable and recommends approval. I agree that there are no outstanding clinical pharmacology issues that would preclude approval. Due to NB's potential to inhibit the activity of Organic Cation Transporter 2 (OCT2), the clinical pharmacology reviewer is recommending that the sponsor conduct an *in-vivo* drug-drug interaction study to evaluate the effect of NB on an OCT2 substrate such as metformin. This will be included in the action letter as a post-marketing requirement.

Given that bupropion and naltrexone have been marketed for more than 25 years without a meaningful signal for proarrhythmic effects, the Division did not require that a thorough QT study be conducted prior to submission of the Contrave NDA. The Agency's interdisciplinary team for QT studies reviewed ECG data from the phase 1 study NB228 and the phase 3 study NB-303 and relevant adverse events from the Integrated Summary of Safety. A search of the Agency's Adverse Event Reporting System (AERS) was also conducted. No large changes in QTc were observed. However, in diabetics, the incidence of QTcF ≥ 30 ms was "slightly higher" in the Contrave 32/360 vs. the placebo group. There were no imbalances between the Contrave and placebo groups in the rates of reporting of adverse events that could be associated with proarrhythmic effects. There were no signals for Torsade or sudden death in AERS. AERS reports QRS prolongation and bundle branch block were associated with bupropion overdose. Taken together, the available data do not raise concern that Contrave is proarrhythmic.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The sponsor is proposing to only market the 8 mg naltrexone/90 mg bupropion dose. The recommended maintenance dose is two tablets twice daily.

Three doses of NB were used in the phase 3 clinical trials: 16 mg naltrexone/360 mg bupropion (NB16), 32 mg naltrexone/360 mg bupropion (NB32), and 48 mg naltrexone/360 mg bupropion (NB48). Because NB32 is the proposed maintenance dose, this memorandum focuses on this dose.

The efficacy of NB32 was evaluated in four 56-week phase 3 trials comprising approximately 4500 subjects. Three of the trials, NB-301, NB-302, and NB-303, were conducted in overweight (BMI 27-29.9 kg/m²) and obese (BMI ≥ 30 kg/m²) male and female subjects with or without hypertension and/or dyslipidemia. Trial NB-304 was conducted in overweight and obese subjects with type 2 diabetes. All trials began with a 4-week titration phase.

The majority of the study subjects were Caucasian females. The mean baseline age was approximately 45 years, with half of the subjects between the ages of 45-64 years. Less than 1.0% of the enrolled population had a history of “coronary artery disease,” “myocardial infarction,” or “stroke”.

NB-301 randomized 1:1:1 approximately 1700 subjects to daily NB32, placebo, or NB16 treatment. All subjects received diet instruction and advice on behavior modification and exercise every 12 weeks.

NB-302 randomized 3:1 approximately 800 subjects to daily NB32 or placebo treatment. All subjects received intensive behavioral modification consisting of dietary instruction, prescribed exercise, and 28 group sessions on lifestyle modification. The group behavior modification sessions occurred every week for the first 16 weeks, once every two weeks for the next 12 weeks and monthly thereafter.

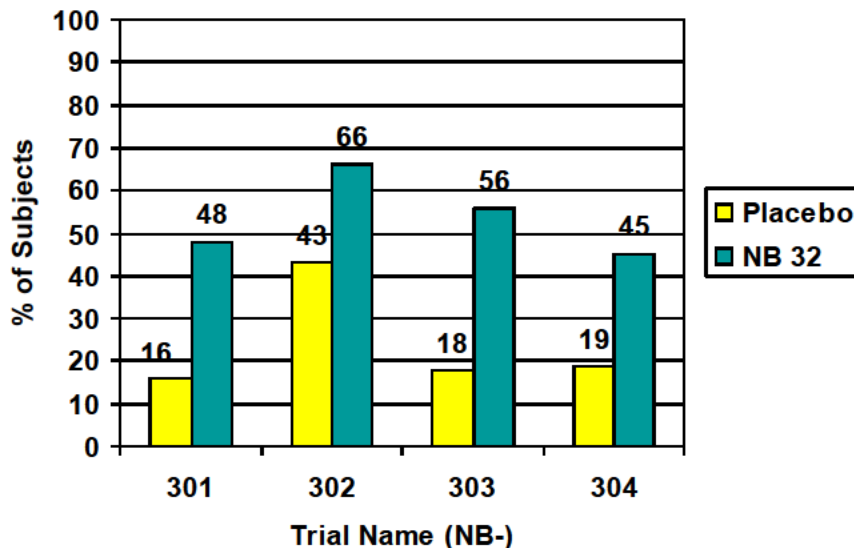
NB-303 randomized 2:1 approximately 1500 subjects to daily NB32 or placebo treatment. At Week 28 subjects on NB32 who failed to lose at least 5% of baseline body weight were re-randomized to continue NB32 or to treatment with 48 mg naltrexone/bupropion 360 mg (NB48). Subjects on NB32 who did not maintain at least a 5% reduction in body weight during Weeks 32-44 were also re-randomized to continue NB32 or NB48. All subjects received diet instruction and advice on behavior modification and exercise every 12 weeks. Given the post-baseline re-randomization process, the Division considers weight loss at Week 28 to be the primary efficacy endpoint for NB-303.

NB-304 randomized 2:1 approximately 500 subjects to daily NB32 or placebo treatment. All subjects received diet instruction and advice on behavior modification every 12 weeks.

All of the following efficacy data are from the modified intent-to-treat population, defined as all randomized subjects who had a baseline measurement and at least one post-baseline measurement while on study drug.

- In NB-301, the mean placebo-subtracted weight change from baseline up to Week 56 was -4.8% in the NB32 group ($p < 0.001$ vs. placebo). The mean placebo-subtracted weight change from baseline up to Week 56 was -3.7% in the NB16 group ($p < 0.001$).
- In NB-302, the mean placebo-subtracted weight change from baseline up to Week 56 was -4.2% in the NB32 group ($p < 0.001$).
- In NB-303, the mean placebo-subtracted weight change from baseline up to Week 28 was -4.6% in the NB32 group ($p < 0.001$).
- In NB-304 (type 2 diabetics), the mean placebo-subtracted weight change from baseline up to Week 56 was -3.3% in the NB32 group ($p < 0.001$).

The proportions of subjects who lost at least 5% of baseline body weight up to Week 56 (Week 28 for NB-303) are shown in the following figure. All NB32 versus placebo group comparisons were of nominal statistical significance.



Forty percent of subjects randomized to NB16 in study NB-301 lost at least 5% of baseline body weight compared with 16% of subjects randomized to placebo ($p < 0.001$).

The weight loss observed in the NB32-treated groups was associated with improvements in levels of HDL-C and triglyceride and measures of glucose and insulin metabolism and HbA1c (in diabetics). Although mean levels of hsCRP decreased by a greater amount in NB32 versus placebo subjects, the difference between groups was of nominal statistical significance only in study NB-301 (Week 28 levels in NB-303 were not statistically significantly different between NB32 and placebo). Compared with placebo-treated subjects, the beneficial effect of weight loss on blood pressure and heart rate was attenuated in subjects treated with NB32.

8. Safety

The safety profiles for naltrexone and bupropion monotherapies are reasonably well known.

Adverse events reported with naltrexone monotherapy include nausea, vomiting, nervousness, anxiety, insomnia, dizziness, headache, and somnolence. At very high doses, naltrexone has been associated with hepatic transaminitis. These findings led the Agency in the mid-1980s to include a boxed warning for liver injury in the naltrexone labeling. However, a recent review by the Office of Surveillance and Epidemiology of data from FDA's Adverse Event Reporting System, published literature, and clinical trials suggests that naltrexone at doses ≤ 50 mg per day is not associated with a risk for serious liver injury.

Adverse events reported with bupropion monotherapy include agitation, insomnia, headache, nausea, vomiting, constipation, and tremor. Bupropion increases the risk for seizures and is

contraindicated in subjects with seizure disorders. At 300 mg per day, the estimated incidence of seizure is 1/1000 subjects (0.1%). This risk increases almost 10-fold with daily doses of 450 to 600 mg per day. All anti-depressant medications, including bupropion, include a boxed warning for suicidality.

In the NB phase 3 clinical trials, there was one reported death. This occurred in a NB-treated subject who suffered a fatal myocardial infarction. There were very few serious adverse events reported by subjects in the NB or placebo groups. Adverse events that led to drug discontinuation in more NB than placebo subjects were nausea, headache, dizziness, vomiting, insomnia, rash, blood pressure increase/hypertension, fatigue, palpitations, abdominal pain, tremor, constipation, diarrhea, feeling jittery, and disturbance in attention. Adverse events reported by 5% or more of NB-treated subjects and at least twice the rate of placebo-exposed subjects were nausea, constipation, vomiting, dizziness, and dry mouth.

Two individuals treated with NB32 (0.06%) suffered a seizure compared to none of the individuals treated with placebo. No subject in the NB development program had serum transaminase and bilirubin elevations that satisfied the criteria for Hy's law nor did any subject develop severe liver injury. Furthermore, there was no meaningful imbalance in the proportion of NB vs. placebo-treated subjects with elevations in hepatic transaminase levels.

There were no completed suicides, suicide attempts, or preparatory acts towards suicide in the NB program. One subject from an NB-treated group (<0.1%) compared with three subjects from the placebo-treated groups (0.2%) was reported to have had suicidal ideation or behavior.

A novel finding noted in Dr. Craig's review was an increase in serum creatinine in subjects treated with NB32. A larger percentage of subjects treated with NB32 compared with placebo had shifts to "high" serum creatinine at any post-baseline assessment. Two subjects randomized to NB32 and one randomized to placebo discontinued therapy due to elevations in serum creatinine, which normalized following study drug withdrawal. There were no reports of renal failure in any subject treated with NB in the phase 3 clinical trials.

Orexigen believes that the change in serum creatinine in NB-treated subjects is due to bupropion and its metabolites' inhibition of renal organic cation transporter 2 (rOCT2). This transporter is found in the basolateral membrane of the renal tubule and promotes creatinine secretion. Results from an *in-vitro* study support the sponsor's assertion regarding the mechanism for increased serum creatinine. At the request of the clinical pharmacology reviewers, the sponsor will be required to conduct an *in-vivo* post-marketing study to further evaluate NB's effect on the rOCT2.

Bupropion, through inhibition of the neuronal reuptake of norepinephrine, may increase sympathetic nervous system activity. This is of potential concern when treating a population of overweight and obese subjects, of whom many already have heightened sympathetic tone. There were small but statistically significant mean increases in blood pressure and pulse in NB- vs. placebo-treated subjects in the phase 3 clinical trials. In addition, there were more adverse events related to hypertension in the naltrexone/bupropion groups, particularly in subjects with type 2 diabetes. The overall number of major adverse cardiac events in these

trials was very small. The NB development program, therefore, does not inform the question of whether long-term treatment of overweight and obese individuals with NB has a positive, neutral, or negative effect on the incidence of cardiovascular disease events.

In 2006, Rigotti et al. reported the results of a study in which 248 smokers were randomized to daily 300 mg of sustained-release bupropion or placebo immediately following admission to the hospital for an acute coronary syndrome. At Week 12, the incidence of cardiovascular events was 16% in the bupropion-treated subjects vs. 14% in the placebo-treated subjects [RR 1.22 (0.64, 2.33)].¹ While the results were not statistically significant, it is concerning that the point estimate for risk favors harm. Furthermore, the results of the study are consistent with more than a 2-fold increase in risk for cardiovascular events in bupropion-treated subjects.

The recently completed Sibutramine Cardiovascular Outcomes (SCOUT) trial found that obese subjects treated with 10-15 mg per day of sibutramine vs. placebo for a mean of 3.5 years had a 16% increase in the relative risk for the composite endpoint of major adverse cardiac events.² The incidence of death due to coronary heart disease events did not differ between treatment groups, but the relative risks for non-fatal myocardial infarction and non-fatal stroke were 28% and 36% higher, respectively, in the sibutramine-treated subjects. Absent a definable subgroup of subjects in whom sibutramine's potential benefits outweighed its potential risks, the drug was removed from the United States market in October 2010.

Although the relative increases of blood pressure and pulse with sibutramine are larger than those associated with NB, the results from the SCOUT trial and the ultimate fate of sibutramine must be taken into account when considering the cardiovascular safety profile of NB.

9. Advisory Committee Meeting

On December 7, 2010, the efficacy and safety data from the NB program were discussed with an Agency advisory committee. The committee voted 13 "yes" and 7 "no" in response to the question of whether the potential benefits of NB outweigh the potential risks when used long-term in a population of overweight and obese individuals. In response to the question of whether a clinical trial designed to examine NB's effect on risk for cardiovascular disease events should be conducted before or after approval, eight members of the committee voted "prior to approval," 11 voted "after approval," and one member abstained. Two of the 11 panelists who voted in favor of conducting the cardiovascular outcomes trial post-approval voted "no" to the question of whether the potential benefits of NB outweigh the potential risks.

10. Pediatrics

¹ Rigotti N et al. Bupropion for smokers hospitalized with acute cardiovascular disease. 2006 *The Amer J Med.* 119:1080-1087.

² James, T et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. 2010 *N Engl J Med.* 363:905-917.

The sponsor requested a waiver of pediatric studies in subjects [REDACTED] (b) (4) [REDACTED] Since the application is not being approved this review cycle, details of the proposed pediatric plan will be addressed in consultation with PeRC at a later date.

11. Other Relevant Regulatory Issues

Dr. Craig notes that there were two clinical investigators from the NB development program who had disclosable financial arrangements with the sponsor. Given the number of subjects enrolled by these two investigators relative to the total number of subjects enrolled in the phase 3 clinical trials, it is very unlikely that they could have materially affected the overall NDA review findings.

Routine inspection of clinical sites by the Division of Scientific Investigation did not uncover any major deficiencies or irregularities in the reporting of data. Their overall assessment was that the phase 3 clinical data provided in the NDA should be considered reliable.

12. Labeling

In a consultative review, the Agency's Study Endpoints and Labeling Development reviewer recommended against inclusion in the labeling of data generated from the Impact of Weight on Quality of Life and the Control of Eating questionnaires. The sponsor did not provide adequate evidence to document content validity. Recommendations to address these deficiencies will be provided in the action letter as non-approvability issues.

Because the application will receive a complete response action, there were no labeling reviews or negotiations with the sponsor.

13. Decision/Action/Risk-Benefit Assessment

In the three trials appropriately designed to evaluate weight loss of NB compared with placebo over the course of one year, NB32, the maintenance dose proposed for marketing, was associated with an average of -3.3% to -4.8% reduction in body weight. In these trials, 16% to 43% of subjects treated with placebo lost at least 5% of baseline body weight compared with 45% to 66% of subjects treated with NB32. In general, NB-associated weight loss was accompanied by favorable changes in serum levels HDL-C, TG, insulin, glucose, and HbA1c. The expected weight-loss induced reductions in blood pressure and pulse, however, were attenuated by treatment with NB32.

While there are no head-to-head studies comparing the weight loss effects of NB32 to sibutramine, across-study comparisons suggest that their efficacy profiles are similar. The pressor effects of NB32 appear to be less pronounced than those of sibutramine. Nonetheless, in the wake of the SCOUT study, the most prudent path forward would be to require a pre-approval cardiovascular outcomes trial to obtain a true estimate of NB32's effect on the

incidence of major adverse cardiac events. Data from such a trial will allow for a more comprehensive assessment of NB32's long-term risk-benefit profile.

I agree with Dr. Craig's recommendation that, pending the results from a cardiovascular outcomes study, this NDA receive a Complete Response action.

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
01/31/2011