FDA Briefing Document

NDA 200063

Contrave (Naltrexone 4mg, 8mg/Bupropion HCL 90mg extended release tablet)

Sponsor: Orexigen Therapeutics Inc.

Advisory Committee – December 7, 2010

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 9 November 2010

FROM: Eric Colman, MD
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TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 7 December 2010, Advisory Committee meeting for naltrexone/bupropion (Contrave)

Background

Thank you for agreeing to participate in the December 7, 2010, advisory committee meeting. This meeting is being held to discuss the efficacy and safety of a fixed-dose combination of naltrexone and bupropion (NB) for weight loss. Naltrexone, an opioid antagonist, was approved for opioid addiction in 1984 and for alcohol dependence in 1995. Bupropion, an inhibitor of neuronal uptake of norepinephrine and dopamine, was approved for depression in 1985, smoking cessation in 1997, and seasonal affective disorder in 2006.

Orexigen, the company developing NB, is seeking approval of the following indication:

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/m^2 or ≥27 kg/m^2 with one or more risk factors (e.g. diabetes, dyslipidemia, or hypertension).

Proposed Dosing Regimen

Orexigen is proposing the following dosing regimen for NB (proposed tradename CONTRAVE):

The recommended daily dose of CONTRAVE is two 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion.

CONTRAVE dosing should be escalated according to the following schedule:

	Morning Dose	*Evening Dose*
Week 1	*One CONTRAVE 8/90 tablet*	----------
Week 2	*One CONTRAVE 8/90 tablet*	*One CONTRAVE 8/90 tablet*
Week 3	*Two CONTRAVE 8/90 tablet*	*One CONTRAVE 8/90 tablet*
Week 4 – Onward (maintenance dose)	*Two CONTRAVE 8/90 tablet*	*Two CONTRAVE 8/90 tablet*

The total daily maintenance dose of two CONTRAVE 8/90 tablets twice a day 32/360 is reached at the start of Week 4.

CONTRAVE should be taken by mouth in the morning and in the evening. The tablets should not be cut, chewed, or crushed. Doses above 32/360 mg (4 tablets daily) are not recommended.

Treatment initiation and escalation with CONTRAVE 4/90 tablets may be considered. If well tolerated, patients using CONTRAVE 4/90 tablets should switch to CONTRAVE 8/90 tablets to have their daily dose increases to the recommended daily dose of 32 mg naltrexone and 360 mg bupropion (two CONTRAVE 8/90 tablets twice daily) to maximize weight loss.

Draft Guidance

In 2007 the Division issued a draft guidance entitled Developing Products for Weight Management. The guidance stipulates that a drug will be considered effective if at least one of the following criteria is satisfied after one year of treatment:

1. 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

or

2. 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

Efficacy of NB

Phase 3 Study Design

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/m^2) and obese (BMI $\geq$ 30 kg/m^2) 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.

Efficacy: Mean and Categorical

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.

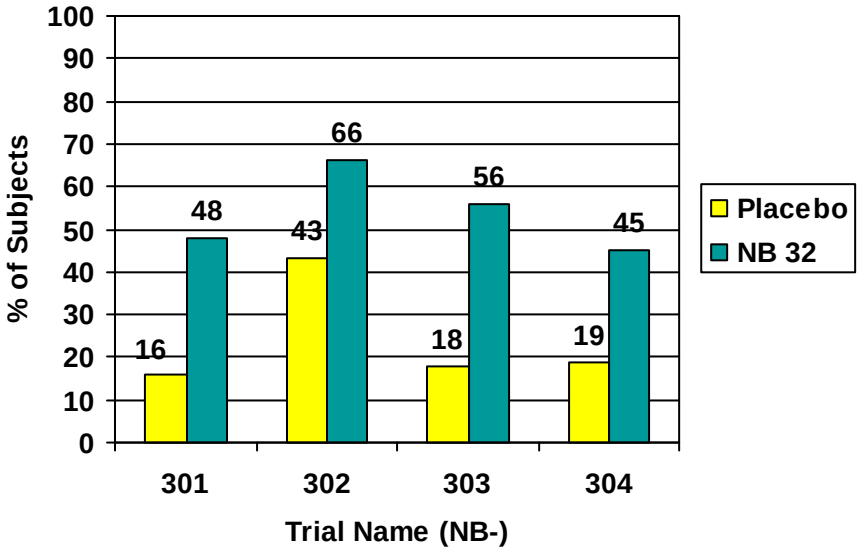
- In NB-301, the mean placebo-subtracted weight change from baseline up to Week 56 was -4.8% in the NB32 group ($p<0.001$ vs. placebo). The mean placebo-subtracted weight change from baseline up to Week 56 was -3.7% in the NB16 group ($p<0.001$).

- 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.

When gauged by the standards of the Division's 2007 draft guidance for Developing Products for Weight Management, NB32 did not satisfy the mean efficacy criterion. NB32 did satisfy the categorical efficacy criterion in studies NB-301 (nondiabetics) and OB-304 (type 2 diabetics). The categorical efficacy criterion for NB32 was not met in NB-302 (intensive lifestyle modification). Because some subjects were re-randomized prior to Week 56 in study NB-303, it is difficult to draw accurate conclusions about the long-term efficacy of NB32 from this trial. NB16 did not satisfy the mean efficacy criterion but did satisfy the categorical efficacy criterion.

Safety of NB

The safety assessment of NB includes, but is not limited to, cardiovascular safety, seizures, psychiatric/cognitive adverse events, and increases in serum creatinine.

Cardiovascular Safety

Bupropion, as an inhibitor of neuronal reuptake of norepinephrine, has the capacity to increase blood pressure and pulse. In the NB phase 3 clinical trials, subjects treated with NB32 had small but statistically significant mean increases in systolic and diastolic blood pressure and pulse rate relative to placebo. The treatment effect was most pronounced during the first eight weeks of treatment. NB32-treated subjects who lost at least 5% of baseline body weight (i.e., responders) had more favorable changes in blood pressure and pulse than NB32 nonresponders, but placebo responders had the most favorable changes overall in blood pressure and pulse. The frequency of hypertension-related adverse events was significantly higher in NB32 compared with placebo subjects.

Given the study subject demographics, and the size and duration of the phase 3 studies, the number of major adverse cardiac events (MACE) was too small to make reliable inferences about NB's effect on cardiovascular risk. A rigorous assessment of NB's cardiovascular risk profile would require a dedicated study in an appropriate population of overweight and/or obese individuals. The Division and Orexigen are in the early stages of discussing the design elements of such a study.

Seizures

Bupropion dose-dependently increases the risk for seizures and is contraindicated in people with a seizure history. At bupropion doses of 100 to 300 mg per day, the incidence of seizure is estimated to be approximately 1 in 1000 individuals (0.1%). Two subjects randomized to NB32 (~0.08%) experienced seizures compared with none of the subjects randomized to placebo. History of seizures was an exclusion criterion for the NB clinical trials. Factors believed to reduce the risk for bupropion-associated seizure include limiting the daily dose < 400 mg, administering the drug in divided doses, and initiating therapy with dose titration, all of which were done in the NB phase 3 trials. Individuals with bulimia or anorexia nervosa are believed to be at heightened risk for bupropion-related seizures. The drug is contraindicated in this population.

Psychiatric- and Cognitive-Related Adverse Events

All antidepressants, including Wellbutrin, a bupropion product, carry a boxed warning for increased risk of suicidality when used to treat children, adolescents, and young adults with major depressive disorders or other psychiatric disorders. All marketed bupropion products also carry a boxed warning for serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide in subjects taking the drug in an attempt to quit smoking.

Based on a retrospective assessment of adverse event data, there were no reports of completed or attempted suicide in the NB Phase 3 trials. Three placebo subjects (0.2%) and one NB subject (<0.1%) reported adverse events considered to represent suicidal ideation.

The incidence rates for psychiatric-related adverse events were 12.9% in placebo-treated subjects and 17.6% in NB32-treated subjects. Sleep disorders represented the greatest percentage of psychiatric-related events (11.4% for NB32 versus 7.1% for placebo). Depression was reported by 2.9% of subjects randomized to NB32 compared with 3.4% of subjects randomized to placebo. Anxiety-related adverse events were reported by more NB32 versus placebo subjects (6.6% vs. 4.4%).

Cognitive-related adverse events such as problems with attention and memory impairment were reported infrequently overall; however, three times more subjects treated with NB32 reported these types of adverse events compared with subjects treated with placebo.

Serum Creatinine

Small mean increases in serum creatinine were observed in subjects treated with NB32 compared with placebo. 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.

Draft Discussion Points and Voting Questions

As you read the background documents from the FDA and Orexigen Pharmaceuticals please keep in mind the following draft discussion points and voting questions.

Taking into account the material provided in the background documents and presented at the advisory committee meeting, please comment on whether you believe that the sponsor has:

1. Provided adequate evidence to establish NB's efficacy as a weight-loss drug?

    a. Are there additional studies that you would recommend pre- or post-approval to further evaluate NB's efficacy?

2. Adequately assessed and characterized the potential risk for psychiatric and cognitive-related adverse events such as suicidality, sleep disorders, and memory impairment?

    a. Are there additional studies that you would recommend pre- or post-approval to further assess this risk?

    b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

3. Adequately assessed and characterized the potential for seizures?

    a. Are there additional studies that you would recommend pre- or post-approval to further assess this risk?

    b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

4. Adequately assessed and characterized the potential clinical significance of increases in serum creatinine?

    a. Are there additional studies that you would recommend pre- or post-approval to further assess this risk?

    b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

5. Adequately assessed and characterized the effect of NB on blood pressure and pulse?

    a. Are there additional studies that you would recommend pre- or post approval to further characterize NB's effect on blood pressure and pulse?

    b. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

6. Taking into account NB's effect on blood pressure and pulse, please vote whether you believe a dedicated study to examine the drug's effect on risk for major adverse cardiac events should be conducted: (VOTE)

a. Prior to approval

b. As a post-approval requirement

7. Taking into account the information provided in the background documents, the presentations made at this advisory committee meeting, and your response to question 6, please vote whether you believe that the available data adequately demonstrate that the potential benefits of NB outweigh the potential risks when used long-term in a population of overweight and obese individuals and support approval? (VOTE)

    a. If voting ‘Yes’ please provide your rationale and comment on the need for and approach to post-approval risk management.

    b. If voting ‘No’ please provide your rationale and comment on what additional clinical would be required to potentially support approval.

Clinical Briefing Document
Endocrine and Metabolic Drugs Advisory Committee Meeting
December 7, 2010
New Drug Application 200063:
Contrave® (naltrexone HCl and bupropion HCl) Extended-Release Tablets
Applicant: Orexigen Therapeutics
Clinical Reviewer: Eileen Craig, MD

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1 Executive Summary

1.1 Background

Contrave® is a fixed-dose combination of bupropion (a norepinephrine and dopamine reuptake inhibitor) and naltrexone (a mu-opioid receptor antagonist) developed by Orexigen Therapeutics for the chronic treatment of obesity. Bupropion monotherapy was approved for the treatment of depression in 1985, smoking cessation in 1997, and seasonal affective disorder in 2006. Naltrexone monotherapy was approved in 1984 for the treatment of opioid addiction and for alcohol dependence in 1995.

The long-term efficacy and safety of Contrave (also referred to as naltrexone/bupropion or NB in this document) were assessed in four placebo-controlled one-year trials in overweight and obese subjects receiving customary diet and behavioral counseling (Trials NB-301 and NB-303), in obese subjects undergoing intensive lifestyle modification counseling (Trial NB-302), and in obese subjects with type 2 diabetes (Trial NB-304). Approximately 3200 individuals randomized to NB and ~1500 individuals randomized to placebo, with body mass index (BMI) $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with at least 1 weight-related co-morbidity (e.g., hypertension, dyslipidemia, diabetes), were evaluated in these trials. The efficacy of NB was evaluated using the co-primary endpoints of mean change from baseline in body weight at endpoint and the proportion of individuals who achieved a $\geq$5% reduction in body weight at endpoint.

The proposed indication for NB is the treatment of obesity and weight management, including weight loss and maintenance of weight loss, in conjunction with lifestyle modification. NB is proposed for patients with an initial body mass index $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension).

The proposed NB dose for marketing is two 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion (NB32). A lower dose of two 4/90 tablets taken twice daily for a total dose of 16 mg naltrexone/360 mg bupropion (NB16) is also proposed for those not tolerating the 32 mg naltrexone/360 mg bupropion dose during the escalation or early maintenance period.

In 2007 the Division issued a draft guidance entitled Developing Products for Weight Management. The guidance stipulates that a drug will be considered effective if at least one of the following criteria is satisfied after one year of treatment:

1 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

or

2 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

1.2 Efficacy Summary

The majority of the trial subjects were middle-aged Caucasian women. Elderly individuals (≥65 years) represented 2% of the total trial population. Approximately 25% of individuals had extreme obesity (≥40 kg/m^2), 10% had diabetes, 10% had a history of depression and <1% had a history of cardiovascular disease. Approximately 55%, 51%, and 55% of individuals in the placebo, low-dose and high-dose treatment groups, respectively, completed the 56 weeks of treatment on study drug. For the NB group, adverse events were the major reason for failure to complete the trials. Twelve percent of placebo subjects, 20% of low-dose and 24% of high-dose NB-treated subjects withdrew from the trials due to an adverse event. All of the trials were conducted in the United States.

In all four Phase 3 trials, NB32 (and NB16 in trial NB-301) 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.

- In the pooled dataset, the difference in mean weight loss between NB32 and placebo-treated groups was 4.2% (range: 3.3 to 4.8%).
  - *Non-diabetic pooled groups:* The difference in mean weight loss between NB32 and placebo-treated groups was 4.5% (range: 4.2 to 4.8%).
  - *Diabetic groups:* The difference in mean weight loss between NB32 and placebo-treated groups was 3.3%.
- The difference in mean weight loss between NB16 and placebo-treated groups was 3.7%.

However, these weight loss results do not meet the first criteria set out in the 2007 draft guidance that stipulates that after one year of treatment 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.

In all four Phase 3 trials there was a greater proportion of subjects treated with NB32 (and NB16 in Trial NB-301) who achieved ≥5% weight loss from baseline compared with the placebo group.

	Treatment group	**Number (%) of 5% responders**	**Odds ratio vs placebo (95% CI)**
NB-301 Wk 56	Placebo	84 (16.4%)	--
	NB16	186 (39.5%)	3.4 (2.5, 4.6)
	NB32	226 (48.0%)	4.9 (3.6, 6.6)
NB-302	Placebo	82 (42.5%)	--

	Treatment group	Number (%) of 5% responders	Odds ratio vs placebo (95% CI)
Wk 56	NB32	320 (66.4%)	2.9 (2.0, 4.1)
NB-303 Wk 28	Placebo	80 (17.5%)	--
	NB32	459 (55.6%)	6.6 (5.0, 8.8)
NB-304 Wk 56	Placebo	30 (18.9%)	--
	NB32	118 (44.5%)	3.4 (2.2, 5.5)

With the exception of Trial NB-302 which employed a more intensive behavioral/lifestyle modification program, the proportion of subjects who lost greater than or equal to 5 percent of baseline body weight in the active-product group was at least 35 percent, was approximately double the proportion in the placebo-treated group, and the difference between groups was statistically significant. This meets the FDA's second criteria for efficacy. Thus, per the efficacy criteria outlined in the Division's 2007 draft guidance, both doses of NB were efficacious for weight loss.

Analysis of Secondary Efficacy Endpoints

NB-treated groups had the expected weight loss-related improvements in lipids and glycemia but not in blood pressure.

Analyses of these and other endpoints were conducted at Week 56 for Trials NB-301, NB-302 and NB-304, and at Week 28 for NB-303. Secondary endpoints included the following:

- Subjects (Full Analysis Set, LOCF) who achieved ≥10% decrease from baseline in body weight.
  - A statistically significant greater proportion of NB subjects achieved ≥10% weight loss compared with placebo

	NB-301			**NB-302**		**NB-303**		**NB-304**	
Duration	56 weeks			56 weeks		28 weeks		56 weeks	
	Placebo	NB16	NB32	Placebo	NB32	Placebo	NB32	Placebo	NB32
N	511	471	471	193	482	456	825	159	265
≥ 10% Weight Loss	7.4%	20.2%*	24.6%*	20.2%	41.5%*	7.0%	27.3%*	5.7%	18.5%*

* $p<0.001$ vs. placebo

- 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 [range of Least Squares Mean (LS Mean) difference from placebo: 2.1 to 3.8 cm]
- Lipid parameters (HDL, LDL, triglycerides) change from baseline to endpoint.

  - 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.[1]
  - 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 LS Mean treatment differences from placebo ranged from a decrease of 0.4 to 4.4 mg/dL.
- Glucose and insulin parameters change from baseline to endpoint.
  - Improvements in fasting glucose from baseline were greater for the NB group compared with placebo but were only statistically significant for the NB32 dose in Trial NB-301. In NB-301, the LS mean difference from placebo was -1.9 mg/dL.
- Glycemic control in patients with type 2 diabetes (NB-304 only)
  - At endpoint, subjects receiving NB32 had statistically significantly greater decreases from baseline in HbA1c as compared to subjects receiving placebo (-0.63% for NB32 vs. - 0.14% for placebo; $p<0.001$).
  - The proportion of subjects requiring rescue medications for poor hyperglycemic control in the NB32 group was lower than the placebo group (22.3% NB32 vs. 35.2% placebo)
  - There were few subjects in each group with either dose reductions in oral hypoglycemic medication (1.3% placebo, 1.9% NB32), dose increases (1.3% placebo; 3.0% NB32), or who discontinued investigational therapy due to poor glycemic control (1.9% placebo; 0.0% NB32).
- Systolic and diastolic blood pressure
  - Pulse: At Wks 4 and 8, the Total NB group had a statistically significant difference from placebo of +2.1 bpm. By Wk 56, the statistically significant difference from placebo was +1.4 bpm
  - SBP: At Wks 4 and 8, the Total NB group had a statistically significant difference from placebo of +2.4 mm Hg. By Wk 56, the statistically significant difference from placebo was +1.5 mm Hg.
  - DBP: 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.
  - 24-hour ABPM substudy: At Week 52, the treatment difference for NB32 vs Placebo was +2.6 mm Hg for SBP and +2.9 mm Hg for DBP
- Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire
  - None of the studies showed a clinically meaningful difference between NB and placebo in the IWQOL-Lite total score.

1 For triglycerides, examination of the distribution of baseline values indicated a skewed distribution such that the assumptions underlying regression analyses were not met. The data on fasting triglycerides levels were analyzed by the sponsor using a log 10 transformation of data.

1.3 Safety Summary

The safety assessment of naltrexone/bupropion was focused on concerns known to occur with the marketed monotherapy components naltrexone and bupropion, as well as relevant safety findings that arose in other obesity agents developed in the past. There are five areas of particular interest for safety: blood pressure and pulse, cardiovascular events, seizures, psychiatric-related adverse events and neurologic/cognitive adverse events.

Blood Pressure and Pulse
Hypertension, in some cases severe and requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension. In the NB development program, there were more adverse events related to hypertension in the NB group compared to placebo, particularly in the trial done in individuals with type 2 diabetes. In that trial, 12.0% of subjects in the NB32 group and 6.5% in the placebo group had a blood pressure-related adverse event during double-blind treatment and 10% of the events in the NB32 group were severe compared to 0 in the placebo group.

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.

At Week 52 in the average 24-hour Ambulatory Systolic and Diastolic Blood Pressure substudy (ABPM), the treatment difference for NB32 vs Placebo was +2.6 mm Hg for SBP and +2.9 mm Hg for DBP. The treatment differences for average daytime ABPM systolic and diastolic blood pressures between the NB32 group and placebo were systolic: 3.3 mm Hg and diastolic: 3.1 mm Hg. The difference for blood pressure load between NB32 and placebo was 5%. All differences between NB32 and placebo were statistically significant.

NB attenuates or eliminates the blood pressure and pulse reductions that are normally seen with weight loss. It is not known how these vital sign changes in the overweight and obese population would impact cardiovascular risk over the long term.

Cardiovascular Events
Major cardiovascular (CV) events were defined by the sponsor (but not adjudicated) as cardiovascular death, myocardial infarction, and cerebrovascular accident. There was one death in the NB clinical program, attributed to myocardial infarction in an NB-treated subject. Two additional subjects, both in the NB32 group, experienced a myocardial infarction and one placebo subject experienced a cerebrovascular accident. An additional subject, in the NB16 group, experienced a post-treatment myocardial infarction 36 days after discontinuing study drug.

Few elderly individuals or subjects with a history of myocardial infarction or stroke were enrolled into the phase 3 clinical trials. Not surprisingly, then, the overall number of ischemic cardiovascular-related adverse events in the NB development program was very low. Thus, cardiovascular risk with NB cannot be adequately assessed due to the small number of ischemic CV events in the database and the very limited number of individuals with known CV disease at baseline in the development program.

Seizure and Convulsions
According to the prescribing information for bupropion, bupropion is contraindicated in patients with a seizure disorder. The seizure rate associated with doses of sustained-release bupropion up to 300 mg/day is approximately 0.1% (1/1,000). Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (4/1,000) in depressed patients treated at doses in a range of 300 to 450 mg/day. The risk of seizure appears to be strongly associated with dose. Because the use of bupropion is associated with a dose-dependent risk of seizures, clinicians are advised not to prescribe doses over 300 mg/day for smoking cessation. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures occurred after several weeks at fixed dose. The risk of seizure is also related to patient factors, clinical situations, and concomitant medications.

In the NB Phase 3 trials, two subjects (2/3239, 0.06%) in the NB32 group, compared to none in the placebo group, experienced a seizure. Both subjects had no prior seizure history; one subject may have experienced a hypoglycemic seizure. Of note, individuals with a seizure history or at increased risk for seizures were excluded from the trials.

Psychiatric Events (Suicide-related Events, Depression, Anxiety, Sleep Disorders, Psychosis)
Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, confusion, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses.

Suicide-related Events
A retrospective assessment tool of suicidality, the Columbia Classification Algorithm of Suicide Assessment (C-CASA) was used to assess adverse events that could represent suicidal events (behavior and ideation) during naltrexone/bupropion Phase 2b and 3 trials. There were no completed suicides, suicide attempts, or preparatory acts toward imminent suicidal behavior in any treatment group. There were four events of suicidal ideation or behavior during this trial, one event (1/3239, <0.1%) in the Total NB treatment group compared to three events (3/1515, 0.2%) in the placebo treatment group.

Depression, Anxiety, Sleep Disorders, Psychosis
In the naltrexone/bupropion Phase 3 trials, there were a higher percentage of subjects with psychiatric events in the Total NB group compared with the placebo group (20.8% and 15.5%,

respectively). Psychiatric events were seen more often in subjects with a prior history of depression or anxiety in both Total NB and placebo groups than in subjects without a prior history. Despite bupropion's indication as an anti-depressant, the incidence of depression was similar between treatment groups (6.0% Total NB and 5.9% placebo). However, the incidence of anxiety was greater in the Total NB group compared to placebo [(5.7%) and (4.4%), respectively]. The incidence of sleep disorder adverse events was higher in the Total NB group compared with placebo (12.8% Total NB and 8.4% placebo). Insomnia was the most frequently occurring event (8.6% Total NB and 5.9% placebo) in the Sleep Disorders category. The adverse event incidence in the Psychosis disorders category was higher in the Total NB group compared with placebo (0.8% Total NB and <0.1% placebo). The placebo group had only one report of potential psychosis (depersonalization) and no reports of psychosis events. Of the Total NB subjects with events in the Psychosis category, 18/26 reported either dissociation (10) or agitation (8).

Neurologic/Cognitive
Adverse events involving attention, dizziness and syncope occurred more often in individuals randomized to NB as compared to placebo. There was a greater incidence of Cognitive subtopic events overall (5.1% vs. 2.0%) and Cognitive subtopic events leading to discontinuation (1.1% vs. 0.4%) in the Total NB group compared to the placebo group. None of the events were serious. The most common Cognitive events category was Attention Disorders (2.3% Total NB vs 0.6% placebo). Events in the Dizziness/Syncope subtopic were common in Total NB (10.2%) and 2.8 times more frequent than in placebo (3.6%). The single preferred term dizziness accounted for almost all reported events (10% Total NB and 3.4% placebo). Dizziness was the primary reason for discontinuation in 1.3% of Total NB and 0.3% of placebo subjects. Two NB subjects reported a serious adverse event of syncope and three NB subjects discontinued due to syncope compared to none in placebo.

Renal Function
Larger mean increases in creatinine from baseline to endpoint were observed in the Total NB group compared with the placebo group (0.07 mg/dL NB vs 0.01 mg/dL placebo) and from baseline to maximum (0.15 mg/dL NB vs 0.07 mg/dL placebo). The highest mean serum creatinine levels were seen at Week 4. Shifts to high creatinine[2] at any postbaseline assessment occurred in a higher percentage of subjects in the Total NB group (7.6%) compared with the placebo group (1.9%). However, renal disorder serious adverse events and discontinuations were infrequent.

Hepatobiliary
According to the naltrexone prescribing information, naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be five-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses. According to the bupropion prescribing information, bupropion should be used with caution in patients with hepatic impairment (including mild-to-moderate hepatic cirrhosis) and a reduced frequency

2 A treatment-emergent high value was defined as a change from a value at baseline that is ≤ULN at baseline to a value >ULN at any postbaseline assessment

and/or dose should be considered in patients with mild-to-moderate hepatic cirrhosis. In the NB development program, no subjects met criteria for Hy's law classification[3] and transaminase level increases were similar between treatment groups. There were more gallbladder-related serious adverse events in the Total NB group (0.3%) as compared to placebo (<0.1%). All subjects with gallbladder-related serious adverse events were hospitalized and underwent gallbladder surgery.

2 Introduction and Regulatory Background

2.1 Product Information

Contrave® is a fixed-dose combination of bupropion (a norepinephrine and dopamine reuptake inhibitor) and naltrexone (a mu-opioid receptor antagonist) for the chronic treatment of obesity.

Bupropion hydrochloride was first approved in the US in 1985 for the treatment of depression. Bupropion is currently marketed as three formulations (an immediate-release (IR) tablet formulation [Wellbutrin®], sustained-release (SR) tablet [Wellbutrin SR®], and an extended-release (XL) tablet [Wellbutrin XL®]) for the treatment of depression and seasonal affective disorder as well as under the trade name Zyban® as an aid to smoking cessation treatment (approved 5/97). The usual adult dose for Wellbutrin SR is 300 mg/day and the maximum dose is 400 mg/day, given in divided doses of not more than 200 mg each. Because of the dose-dependent risk of seizures, for smoking cessation, dose is limited to ≤ 300 mg/day (usual dose 150 mg twice daily). Generic versions of each formulation have been approved by the FDA.

Naltrexone HCl was approved in the US in 1984. Naltrexone IR is currently approved for the treatment of opioid addiction (1984) and alcohol dependence (1995) (ReVia® [formerly Trexan®] and Depade®). The usual adult dose for oral naltrexone is 50 mg/day. In 2006, naltrexone free base was approved in the US as an XL injectable suspension (Vivitrol®) for the treatment of alcohol dependence.

The applicant's rationale for the development of this combination product is that administration of naltrexone combined with bupropion will result in greater weight loss than either treatment alone. The applicant states that bupropion stimulates hypothalamic pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (MSH), which in turn binds to and stimulates post-synaptic hypothalamic melanocortin 4(MC4) receptors. The applicant predicts that this profile will promote satiety, reduce feeding, and enhance energy expenditure.

3 Hy's Law: (1)The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.
(2) Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN). (3) No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Final, July 2009

POMC neurons contain an autoinhibitory binding site which, when stimulated, counters an increase in the POMC firing (alpha-MSH secretion). Beta endorphin, a cleavage by-product of POMC and secreted concurrently with alpha-MSH, is the endogenous ligand at this site. The applicant maintains that they have shown in a preclinical model that an opioid antagonist can block this autoinhibitory site and promote and sustain an enhanced rate of POMC firing, which exceeds that seen with bupropion alone. The hypothesis is that pairing the mu-opioid receptor antagonist naltrexone with bupropion will yield a more potent sustained effect on food intake than either agent alone.

The applicant proposes the naltrexone SR/bupropion SR tablets (NB or Contrave) for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, in conjunction with lifestyle modification. NB tablets are proposed for patients with an initial body mass index ≥30 kg/m^2 or ≥27 kg/m^2 with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension). NB drug product is provided as tablets containing either 4 mg or 8 mg of naltrexone HCl and 90 mg of bupropion HCl (4 mg/90 mg tablet and 8 mg/90 mg tablet). The proposed dose for marketing is two NB 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion. NB dosing is escalated over a 3-week period until achieving the total daily maintenance dose of 32 mg naltrexone and 360 mg bupropion. Treatment initiation and escalation with NB 4/90 tablets is also proposed.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: FDA-approved Medications for Weight Management

Drug Trade name/ Generic name	Approval Date	Mechanism of Action/Daily dose range (mg)	Indication
Short-Term Weight Reduction			
ADIPEX-P and Generic/Phentermine hydrochloride	1959	Norepinephrine reuptake inhibitor 15-37.5 mg/day	Indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification, and caloric restriction in the management of exogenous obesity for patients with an initial body mass index (BMI) ≥30 kg/m2, or ≥27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia).
TENUATE and Generic/ Diethylpropion	1959	Norepinephrine releasers 75 mg/day	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial BMI of 30 kg/m^2 or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
BONTRIL; BONTRIL PDM; and Generic/ Phendimetrazine	1959	Norepinephrine releasers 70-210 mg/day	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial BMI of 30 kg/m^2 or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
DIDREX and Generic/ Benzphetamine	1960	Norepinephrine releasers 25-150 mg/day	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial BMI of 30 kg/m^2 or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone

Chronic Treatment of Obesity			
MERIDIA/sibutramine NDA 20632 WITHDRAWN 10/2010	1997	Serotonin-norepinephrine reuptake inhibitor 5-15 mg/day	MERIDIA is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. MERIDIA is recommended for obese patients with an initial BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).
XENICAL/orlistat NDA 20766	1999	Lipase inhibitor 120 mg TID	XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).
ALLI/orlistat (over-the-counter) NDA 21887	2007	Lipase inhibitor 60 mg TID	For weight loss in overweight adults, 18 years and old, when used along with a reduced-calorie and low-fat diet
Source: http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm			

There is currently one obesity medication approved for long-term use in the United States: orlistat. The weight loss efficacy of other obesity medications that have been described at Endocrinology and Metabolism Drug Advisory Committee (EMDAC) meetings are shown in the table below. The tables below present the weight changes in active drug and placebo groups from various Phase 3 trials that are available for comparison.

Table 2: 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 RIO-Europe RIO-Lipids RIO-Diabetes	 -6.5 -6.9 -7.4 -5.5	 -1.7 -2.1 -1.9 -1.6	 -4.7 -4.7 -5.4 -3.9	NDA 21888, statistical review
Qnexa (phentermine/ topiramate) 15/92 mg QD OB-302 (No DM) OB-303 (16% DM)	 -10.9 -9.8	 -1.6 -1.2	 -9.4 -8.6	NDA 22580, FDA Briefing Package, EMDAC meeting, 15 July 2010;NDA 22580 CSR OB-302 Table S1 and CSR OB-303 Table S1
Lorcaserin 10 mg BID APD356-009 BLOOM APD356-011 BLOSSOM (pooled) (No DM)	 -5.9 -5.8 -5.8	 -2.2 -2.8 -2.5	 -3.7 -3.0 -3.3	NDA 22529, Summary of Clinical Efficacy, Table 12 NDA 22529, ISE Table 13

	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**
NB32 (naltrexone 32 mg/bupropion 360 mg) QD				NDA 200063, ISE Table 18
NB-301 (No DM)	-6.1	-1.3	-4.8	
NB-302 (No DM)	-9.3	-5.1	-4.2	
NB-304 (DM)	-5.0	-1.8	-3.3	

Table 3. 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, ISE, post-text Table 33
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	Reference: 4

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients of naltrexone and bupropion are both approved drugs in the US and are both widely available.

The Division of Metabolic and Endocrinology Drug Products (DMEP), in reviewing this NDA for a combination product (bupropion/naltrexone) for the treatment of obesity, requested a utilization analyses from the Office of Surveillance and Epidemiology (OSE). Dr. Borders-Hemphill's review[5] provided an analysis of bupropion and naltrexone concurrency by age, an analysis of outpatient dispensed prescriptions and projected number of patients filling a bupropion or naltrexone outpatient prescription by age, and an analysis of physician reports of diagnoses associated with the use of each product alone and with any additional therapy used to treat the same diagnosis.

Bupropion dispensed prescriptions remained stable (approximately 22 million per year) from year 2005 (21 million prescriptions) to year 2009 (22 million prescriptions), a 6% increase.

4 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. Lancet 2010; 376(9741): 595-605.
5 Borders-Hemphill V NDA 200063 Drug Utilization Review: Naltrexone Bupropion Concurrency July 2010

Across all years studied, bupropion prescriptions were primarily dispensed to patients aged 18-64 years (87%).

Naltrexone dispensed prescriptions increased by 88% from year 2005 (142,000 prescriptions) to year 2009 (267,000 prescriptions) across all age groups. Prescriptions dispensed to patients aged 18-64 years increased by 93% from 122,000 in year 2005 to 234,000 in year 2009 and across all years studied, naltrexone prescriptions were primarily dispensed to this age group (88%).

Concurrent Drug Analysis
Nationally projected number of patients was used to assess concurrency between patients with a claim for bupropion and a claim for naltrexone during each calendar year from 2006 to 2009. Across all years studied, less than 1% of patients in all age groups with a bupropion claim had a concurrent claim for naltrexone. Approximately 13% of patients in all age groups with a naltrexone claim had a concurrent claim for bupropion.

Associated Diagnoses Analysis
According to office-based physician reports from January 2005 through May 2010, weight management, obesity and eating disorders diagnoses associated with the use of bupropion accounted for less than 1% of drug use mentions. For the majority of time, bupropion was used alone to treat these conditions; however, on occasion, topiramate (Topamax®), sertraline (Zoloft®) or escitalopram (Lexapro®) were used concurrently with bupropion to treat some of these conditions.

There were no reports of diagnoses for weight management, obesity and eating disorders associated with the use naltrexone during the time period studied.

2.4 Important Safety Issues With Consideration to Related Drugs

BUPROPION[6] (labeled safety issues for monotherapy, usual dose is 300 mg/day)

Psychiatric: Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, confusion, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses.

Agitation and Insomnia: A substantial proportion of patients treated with bupropion experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of treatment.

6 Wellbutrin SR® (bupropion hydrochloride sustained-release, NDA 20358, date of approval 10/4/96) product label approved on 5/10/2010 and Zyban ® (bupropion hydrochloride sustained-release, NDA 20711, date of approval 5/14/1997) product label approved on 7/1/2009.

Seizures: Bupropion is contraindicated in patients with a seizure disorder. The seizure rate associated with doses of sustained-release bupropion up to 300 mg/day (given as 150 mg twice daily) is approximately 0.1% (1/1,000). This incidence was prospectively determined during an 8-week treatment exposure in approximately 3,100 depressed patients. Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (4/1,000) in depressed patients treated at doses in a range of 300 to 450 mg/day. In addition, the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The risk of seizure appears to be strongly associated with dose. Because the use of bupropion is associated with a dose-dependent risk of seizures, clinicians should not prescribe doses over 300 mg/day for smoking cessation. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose. The risk of seizure is also related to patient factors, clinical situations, and concomitant medications.

- Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, current or prior diagnosis of bulimia or anorexia nervosa, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.
- Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.
- Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.

Allergic Reactions: Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Cardiovascular Effects: In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension. There is no clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. In a group of 36 depressed inpatients with stable congestive heart failure (CHF), bupropion was associated with a rise in supine blood pressure, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

Hepatic Impairment: Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required. Bupropion should be used with caution in patients with hepatic impairment (including mild-to-moderate hepatic

cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild-to-moderate hepatic cirrhosis.

Renal Impairment: Bupropion should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and the metabolites of bupropion may accumulate in such patients to a greater extent than in patients with normal renal function.

Drug-Drug Interactions:
Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity.

- In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between bupropion and drugs that are substrates of or inhibitors/inducers of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel).
- In vitro studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been performed to evaluate this finding.
- While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).
- Although bupropion is not metabolized by the CYP2D6 isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme in vitro. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formal studied. Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.
- Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine.
- Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine.
- Concurrent administration of bupropion and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution.
- In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with bupropion should be minimized or avoided.

Labeled Adverse Reactions: Adverse events commonly encountered in patients treated with bupropion are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes.

Pregnancy: Category C. One study has been conducted in pregnant women. This retrospective, managed-care database study assessed the risk of congenital malformations overall and cardiovascular malformations specifically, following exposure to bupropion in the first trimester compared to the risk of these malformations following exposure to other antidepressants in the first trimester and bupropion outside of the first trimester. This study included 7,005 infants with antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study showed no greater risk for congenital malformations overall or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated.

NALTREXONE[7] (labeled safety issues for monotherapy, usual dose is 50 mg/day)

Hepatic: Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses for the currently approved indications.

Evidence of the hepatotoxic potential of naltrexone is derived primarily from a placebo-controlled study in which naltrexone hydrochloride was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg per day). In that study, 5 of 26 naltrexone recipients developed elevations of serum transaminases (i.e., peak ALT values ranging from a low of 121 to a high of 532; or 3 to 19 times their baseline values) after three to eight weeks of treatment. Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations of similar magnitude in any of the 24 placebo patients in the same study is persuasive evidence that naltrexone is a direct (i.e., not idiosyncratic) hepatotoxin.

This conclusion is also supported by evidence from other placebo-controlled studies in which exposure to naltrexone hydrochloride at doses above the amount recommended for the treatment of alcoholism or opiate blockade (50 mg/day) consistently produced more numerous and more significant elevations of serum transaminases than did placebo. Transaminase elevations in 3 of 9

7 Revia® (naltrexone hydrochloride, NDA 18932, date of approval 11/20/84) product label approved on 12/2001

patients with Alzheimer's Disease who received naltrexone hydrochloride (at doses up to 300 mg/day) for 5 to 8 weeks in an open-label clinical trial have been reported.

Caution should be exercised when naltrexone hydrochloride is administered to patients with liver disease. An increase in naltrexone AUC of approximately 5-and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported.

Renal Impairment: Naltrexone and its primary metabolite are excreted primarily in the urine, and caution is recommended in administering the drug to patients with renal impairment.

Opioid Analgesics: Naltrexone is contraindicated in patients receiving opioid analgesics or who have a positive urine screen for opioids.

Labeled Adverse Reactions: Adverse events commonly encountered in patients treated with naltrexone include nausea, headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety and somnolence.

Pregnancy: Category C. There are no adequate and well-controlled studies in pregnant women.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of key regulatory interactions is presented below:

IND 68858 meeting on 4/24/06 to discuss the development plan for naltrexone/bupropion

- In a response to Orexigen's proposal to not include class warnings regarding the risk of suicidality in depressed patients receiving antidepressants, FDA responded that Zyban currently carries the class suicidality labeling language and that any warning in the bupropion or naltrexone monotherapy label would appear in the combination product label.
- Orexigen was informed that FDA was concerned about blood pressure and pulse parameters and that they should be carefully monitored in the clinical trial setting.
- FDA recommended inclusion of the following subjects in the phase 3 trials: subjects with a BMI≥27 kg/m^2 with weight-related comorbidities such as hypertension, dyslipidemia, type 2 diabetes, sleep apnea, cardiovascular disease and fatty liver; a representative sample of subjects from the ethnic groups in which the prevalence of obesity is highest; individuals with extreme obesity (BMI>40 kg/m^2); and, because they had been excluded from earlier trials, subjects who smoke.

IND 68858 End-of-Phase 2 meeting on 10/1/2007:

- Studies on drug-drug interactions with hypertensive, diabetic and lipid-altering drugs were recommended.
- Due to the known hypertensive effects of bupropion, FDA recommended 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.

- Given that sibutramine, a weight-loss drug also associated with small-to-modest mean increases in systolic and diastolic blood pressure and pulse rate, was at that time being evaluated in a large cardiovascular outcomes study (SCOUT, see discussion in Section 2.6), FDA conveyed that it is possible, depending on the blood pressure data to be obtained with Orexigen's product, a similar study would be required for a fixed-dose combination of bupropion and naltrexone.
- FDA raised concerns that the data from NB-201 were insufficient to satisfy the requirements for a fixed-dose combination product and that additional data comparing the individual components to the combination product should be obtained to confirm the results observed in NB-201. A discussion followed regarding the role of naltrexone as synergistic to bupropion rather than adding much weight loss efficacy as monotherapy. After continued discussion, the Phase 2 data were accepted as sufficient to support conduct of Orexigen's Phase 3 program of naltrexone/bupropion vs placebo.
- FDA requested that the Columbia Suicide-Severity Rating Scale (C-SSRS) and the Patient Health Questionnaire (PHQ-9) be given to every patient at every visit. Orexigen responded that Phase 3 trials have already started and it would be difficult to insert the C-SSRS at this point. They were using the Inventory of Depressive Symptoms-Self Report (IDS-SR). FDA requested a retrospective assessment of suicidality using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) developed by Dr. Kelly Posner and colleagues.

DMEP feedback (09 June 2009) on IND Serial Numbers 094 and 095

- FDA did not agree with the selection of Week 56 for the primary efficacy weight loss endpoints for trial NB-303. Instead, FDA recommended that Week 28 be used for the primary efficacy weight loss endpoints due to differential re-randomization at Week 28. FDA believed that this differential treatment of the two study arms was likely to introduce bias into the estimate of the efficacy of the naltrexone 36 mg / bupropion 360 mg/day at Week 56. The estimated placebo-adjusted weight loss attributed to naltrexone 36 mg / bupropion 360 may tend to be larger than it actually is in the target population. The weight loss endpoints at Week 56 can be used in supportive analyses.

IND 68858 PreNDA Meeting on 12/14/09:

- FDA repeated that for NB-303, the primary efficacy weight loss endpoint should be at Week 28 and that the weight loss endpoints at Week 56 can be used in supportive analyses. FDA views the Week 56 results in NB-303 to be exploratory in nature, and not primary or secondary endpoints.

2.6 Other Relevant Background Information

Sibutramine (Meridia®) and SCOUT

Meridia (sibutramine 5mg, 10mg, 15mg) was approved by FDA in 1997 for the management of obesity, including weight loss and maintenance of weight loss, in conjunction with a reduced calorie diet. Meridia was only recommended for obese patients with an initial body mass index (BMI) $\geq$ 30 kg/m^2, or BMI $\geq$ 27 kg/m^2 with other risk factors (e.g., diabetes, high cholesterol,

controlled high blood pressure). Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition.

Treatment with sibutramine (5 to 20 mg once daily) is associated with mean increases in blood pressure of 1 to 3 mm Hg and with mean increases in pulse rate of 4 to 5 beats per minute relative to placebo. These findings are similar in normotensives and in patients with hypertension controlled with medication. The effect of sibutramine 15 mg once daily on measures of 24-hour blood pressure was evaluated in 12-week placebo-controlled study. Twenty-six male and female, primarily Caucasian individuals with an average BMI of 34 kg/m^2 and an average age of 39 years underwent 24-hour ambulatory blood pressure monitoring (ABPM). Normal diurnal variation of blood pressure was maintained. The mean changes from baseline to Week 12 in various measures of ABPM are shown in the following table.

Table 4: 24-hour ABPM Changes with Sibutramine

Parameter Mm Hg	**Systolic**			**Diastolic**		
	Placebo	**Sibutramine 15 mg**	**Placebo Subtracted**	**Placebo**	**Sibutramine 15 mg**	**Placebo Subtracted**
Daytime	0.2	3.9	+3.7	0.5	5.0	+4.5
Nighttime	-0.3	4.1	+4.4	-1.0	4.3	+5.3
24-hour mean	-0.1	4.0	+4.1	0.1	5.0	+5.1

In November 2009 FDA issued an early communication about an ongoing safety review of Meridia ® (sibutramine hydrochloride)[8]. Preliminary data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) suggested that patients using sibutramine have a higher number of cardiovascular events (heart attack, stroke, resuscitated cardiac arrest, or death) than patients using placebo[9]. SCOUT[10] began in 2002 and enrolled ~10,000 overweight or obese patients with diabetes or a history of coronary or peripheral vascular disease or stroke, along with other CV risk factors.

In January 2010 the FDA required a contraindication on the drug label, cautioning that sibutramine should not be used in patients with a history of coronary artery disease (e.g., heart attack, angina), stroke or transient ischemic attack, heart arrhythmias, congestive heart failure, peripheral arterial disease, or uncontrolled hypertension (e.g., > 145/90 mmHg).

In January 2010, the European Medicine's Agency's Committee for Medicinal Products for Human Use[11] recommended the suspension of sibutramine and the drug was withdrawn from the European market.

8 Food and Drug Administration. Early communication about an ongoing safety review of Meridia (sibutramine hydrochloride). November 20, 2009.
9 European Medicines Agency. Press release 21 January 2010.
www.ema.europa.eu/pdfs/human/referral/sibutramine/3940810en.pdf.
10 Torp-Pedersen C, Caterson I, Coutinho W, et al. Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial. *Eur Heart J* 2007; 28:2915-2923.
11 European Medicines Agency. Questions and answers on the suspension of medicines containing sibutramine. 21 Jan 2010

In September 2010 published data from SCOUT showed that over a mean 3.4 years of treatment, cardiovascular events (nonfatal MI, nonfatal stroke, resuscitation after cardiac arrest, or cardiovascular death) were reported in 11.4% of patients using sibutramine compared to 10% of patients using placebo [HR 1.16 (95%CI 1.03, 1.31), p=0.015)].[12] There were no significant differences in the cardiovascular death rates and the rate of death from any cause (a secondary outcome) among those on sibutramine compared with those on placebo.

An Advisory Committee meeting was held on 9/15/2010 to discuss the results of SCOUT. Eight of 16 committee members said Meridia (sibutramine) should be withdrawn from the market because its CV risks outweigh the drug's benefits. Of the 8 committee members who voted to keep Meridia on the market, 2 voted in favor of continued marketing with stronger warnings in labeling (to include a boxed warning), while 6 members voted for continued availability with stronger warnings in labeling and an upgraded REMS with elements to assure safe use, such as restricted distribution. Most committee members found the data did not support blood pressure or pulse monitoring as a clear way to mitigate the risk of a CV event. Many committee members said even though Meridia reduces weight, there should be evidence of other accompanying benefit, such as CV benefit or improved glucose parameters.

On 10/07/2010, FDA asked Abbott Laboratories to voluntarily remove Meridia (sibutramine) from the U.S. market because of SCOUT's clinical trial data indicating an increased risk of myocardial infarction and stroke in the studied population. After carefully evaluating the data, FDA was not able to identify a population for whom the benefits of the drug outweighed the risks. Since there was not a population that could be defined, FDA was not able to develop a risk mitigation strategy. In the opinion of the Office of New Drugs and the Office of Surveillance and Epidemiology, until or unless data are submitted showing a population that would clearly benefit, Meridia should not remain on the market. Abbott agreed to withdraw Meridia.

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

3.1 Clinical Pharmacology

There were 15 Phase 1 studies conducted as part of the formulation development and/or clinical pharmacology programs.

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_107/WC500094238.pdf (accessed Aug, 26, 2010).

12 SCOUT Investigators. Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects. N Engl J Med 2010; 363:905-17.

Table 5: Pharmacokinetics of Bupropion and Naltrexone

	Bupropion	Naltrexone
Metabolism / Elimination	Hepatic Metabolism (CYP2B6) Bupropion and its metabolites inhibit CYP2D6 Single dose to healthy subjects: mean T½ elimination half-life was ~ 21 hours. Following twice daily administration: metabolites of bupropion accumulate and reach steady state concentrations in ~ one week. Primarily excreted in urine, 87% of oral dose (~0.5% as unchanged bupropion); fecal elimination is minor (10%)	Cytosolic dihydrodiol dehydrogenase/ Single dose to healthy subjects: mean T½ elimination half-life was ~ 5 hours. Following twice daily administration: naltrexone does not accumulate and its kinetics appear linear. Primarily excreted in urine, 37-60% of oral dose (<2% as unchanged naltrexone); fecal elimination is minor (6.5%)
Food Effect	When NB was given with a high-fat meal the AUC and Cmax for bupropion increased 1.4-fold and 1.8-fold, respectively. At steady state, the food effect resulted in AUC and Cmax increases of 1.1- and 1.3-fold for bupropion, respectively. PI for Wellbutrin SR®: Food increases AUC and Cmax of Bupropion by 17% (1.2 fold) and 11% (1.1 fold), respectively.	When NB was given with a high-fat meal the AUC and Cmax for naltrexone increased 2.1-fold and 3.7-fold, respectively. At steady state, the food effect resulted in AUC and Cmax increases of 1.7- and 1.9-fold for naltrexone, respectively.
Intrinsic Factors Weight, Age, Gender, Race	No clinically meaningful covariate effects have been identified for bupropion pharmacokinetics, however one study suggested elderly subjects are at higher risk for accumulation of metabolites, likely due to trend of decreased renal function with advanced age.	No clinically meaningful covariate effects have been identified for naltrexone pharmacokinetics.
Intrinsic Factors Hepatic Impairment	No significant difference in PK of bupropion or its metabolites in patients with mild to moderate impairment. Severe hepatic cirrhosis resulted in increased bupropion AUC and Cmax (by 70% and 3-fold, respectively) and increased hydroxybupropion AUC by 1.5-fold and combined threohydrobupropion/ erythrohydrobupropion AUC by 2.5-fold.	Naltrexone AUC increased 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively.
Intrinsic Factors Renal Impairment	Bupropion Cmax and AUC values were comparable, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for an inter-study comparison between	Naltrexone peak plasma concentrations were elevated 6- to 28-fold in patients with end-stage renal disease requiring dialysis, compared to historical data in healthy subjects.

	Bupropion	Naltrexone
	patients with end-stage renal failure and healthy subjects.	

Drug Interactions:

Table 6: Pharmacokinetic Drug Interaction Studies Conducted as Part of the NB Clinical Pharmacology Program Assessing Effect of Other Agents on Naltrexone and/or Bupropion

Interacting drug(s)	Test Drug	Effect on Test Drug PK	Mechanism	Source
Atorvastatin	Naltrexone	No Effect	NA	Study NB-232
	Bupropion	No Effect	NA	
Glyburide	Naltrexone	AUC & Cmax ↑1.9-fold & 2.1-fold	Possible food effect (glucose solution)	Study NB-233
	Bupropion	AUC & Cmax ↑ 36% & 18%		
Lisinopril	Naltrexone	No Effect	NA	Study NB-234
	Bupropion	No Effect	NA	
Metoprolol	Naltrexone	AUC & Cmax ↓ 25% & 29%	NA	Study NB-236
	Bupropion	No Effect	NA	
Nifedipine	Naltrexone	AUC & Cmax ↑ 24% & 58%	Possible affect via gastric transit time	Study NB-234
	Bupropion	Cmax ↑ 22%		
Valsartan	Naltrexone	No Effect	NA	Study NB-232
	Bupropion	No Effect	NA	

Glyburide: Co-administration of NB with glyburide resulted in increased AUC and Cmax values of naltrexone of 1.9- and 2.1- fold, respectively, and bupropion 1.4- and 1.2- fold, respectively (see Table 7). Orexigen contends that the glyburide effect is confounded by the coadministration of an oral glucose solution and is thus consistent with the known moderate food effect.

CYP2D6: Bupropion and its metabolites have been shown to inhibit the metabolism of CYP2D6 substrates. In Study NB-236, NB increased metoprolol AUC and Cmax by approximately 4- and 2-fold, respectively, relative to metoprolol alone. Similar clinical drug interactions resulting in increased pharmacokinetic exposure of CYP2D6 substrates have also been observed with bupropion as a single agent with desipramine and venlafaxine. Co-administration of drugs that are metabolized by the CYP2D6 isozyme (e.g., SSRIs and many tricyclics, antipsychotics, beta-blockers, and Type 1C antiarrhythmics) should be initiated at the lower end of the dose range of the concomitant medication.

CYP2B6: Bupropion is primarily metabolized by the CYP2B6 isozyme. Drug interactions may occur between NB and drugs that are substrates of the CYP2B6 isozyme (orphenadrine, thiotepa, and cyclophosphamide).

Drugs that induce Cytochrome P450 enzymes: Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital or phenytoin) leading to potentially reduced efficacy.

4 Sources of Clinical Data

The NB clinical development program is composed of 23 trials, including 15 Phase 1, four Phase 2, and four pivotal Phase 3 trials.

4.1 Tables of Clinical Trials

Table 7: Safety and Efficacy Clinical Trials for NB

Trial Name	Primary Endpoint	Trial Design	Test Product(s): Dosage Regimen	# Enrolled/ # Random-ized	Trial Population	Duration of Treatment
PHASE 2						
OT-101 Phase 2/ Proof-of-Concept	Percent and absolute change from baseline to endpoint in body weight	Multicenter, Randomized, Nal-Blind, PBO-Controlled, Cross-Over (Groups 5 & 6)/	Flu, 60 mg, Capsule, Nal-SR, 50 mg, Caplet, Bup-SR, 150 mg Tablet 1. Flu 60 mg QD + Nal-SR 50 mg QD 2. Flu 60 mg QD+ PB 3. Bup150 mg BID + Nal-SR 50 mg QD 4. Bup-SR 150 mg BID +PBO QD 5. PBO BID + Nal-SR 50 mg QD 6. PBO BID + PBO QD	358/ Placebo: 59 Nal50: 60 B300: 59 Nal50/B300: 60 Crossover: Pbo to Nal50/B300: 18 Nal50 to Nal50/B300: 16	Un-complicated Obesity; Non-smoker (30-40 kg/m2); 18 to 60 years, male and female	Up to 48 Weeks Primary Treatment period 16 weeks Extension/ Crossover Period 32 weeks
NB-201 Phase 2 Dose-finding	Percent and absolute change from baseline to endpoint in body weight	Multicenter, Randomized, Double-Blind, PBO-Controlled Cross-Over (Wk 24; Groups 4, 5 and 6) to Open Label Bupropion and Blinded Naltrexone	Nal-SR 4, 8, and 12 mg tablet Bup-SR, 100 mg tablet Maintenance dose: 1. Bup-SR 200 mg + Nal-SR 24 mg/ BID 2. Bup-SR 200 mg + Nal-SR 8 mg/ BID 3. Bup-SR 200 + PBO/ BID	419/ Placebo: 88 Nal48: 61 B400: 66 Nal16/B400: 67 Nal32/B400: 70 Nal48/B400: 67 Crossover:	Un-complicated Obesity; Non-smoker (30-40 kg/m2); 18 to 60 years, male and female	Up to 48 Weeks Primary Treatment 24 weeks Extension/ Crossover Period 24 weeks

Trial Name	Primary Endpoint	Trial Design	Test Product(s): Dosage Regimen	# Enrolled/ # Random-ized	Trial Population	Duration of Treatment
			4. PBO + Nal-SR 24 mg/ BID 5. PBO + PBO/ BID 6. Bup-SR 200 mg +Nal-SR 16 mg/BID	Placebo to Nal32/B400: 61 Nal48 to Nal32/B400: 34		
NB-201 Sub-study Phase 2	Evaluate change in visceral and total fat	Randomized, Double-Blind, PBO-Controlled	Same as Parent Trial NB-201 (above)	107	Eligible Subjects from the Parent NB-201 Trial	24 weeks
PHASE 3						
NB-301 1st subject enrolled: 10/04/07 Last subject com-pleted: 5/26/09	Percent change from baseline to endpoint in body weight Proportion of subjects with ≥5% weight loss from baseline Trial had a Discontinuation Period	Multicenter, Randomized, Double-Blind, PBO-Controlled	Placebo Naltrexone SR 16 mg/day and Bupropion SR 360 mg/day (NB16) Naltrexone SR 32 mg/day and Bupropion SR 360 mg/day (NB32)	1742/ Placebo: 581 NB16: 578 NB32: 583	Uncomplicated Obesity or Overweight +/- Controlled HTN, +/- Dyslipidemia (27-45 kg/m2); 18 to 66 years, male and female	57-58 weeks Titration Period: 4 weeks Drug Maintenance Period: 52 Weeks Discontinuation Period: 2 weeks
NB-301 Sub-study	Change from baseline in total fat mass	Multicenter, Randomized, Double-Blind, PBO-Controlled	Same as Parent Trial NB-301 (above)	214/ DEXA Placebo: 77 NB16 and 32: 137	Eligible Subjects from the Parent NB-301 Trial	52 week double-blind assessment
NB-302 1st subject enrolled: 03/07/07 Last subject com-pleted: 12/09/08	Percent change from baseline to endpoint in body weight Proportion of subjects with ≥5% weight loss from baseline ;	Multicenter, Randomized, Double-Blind, PBO-Controlled	Placebo Naltrexone SR 32 mg/day and Bupropion SR 360 mg/day (NB32)	793/ Placebo: 202 NB32: 591	Uncomplicated Obesity or Overweight +/- Controlled HTN, +/- Dyslipidemia (27-45 kg/m2); nonsmokers 19 to 65 years, M+F; participated in intense group lifestyle modification counseling (28 sessions)	56 weeks Titration Period: 4 Weeks Drug Maintenance Period: 52 weeks
NB-303 1st subject enrolled: 12/06/07	Percent change from baseline to endpoint in body weight Proportion of subjects with	Multicenter, Randomized, Double-Blind, PBO-Controlled	Placebo Naltrexone SR 32 mg/day and Bupropion SR 360 mg/day (NB32) From Week 28 through Week 44, non-responders	1496/ Placebo: 495 NB32: 1001 Re-randomize	Uncomplicated Obesity or Overweight +/- Controlled HTN, +/- Dyslipidemia (27-45 kg/m2);	56 weeks Titration Period (Fast 4 weeks or Slow 5 weeks)

Trial Name	Primary Endpoint	Trial Design	Test Product(s): Dosage Regimen	# Enrolled/ # Random-ized	Trial Population	Duration of Treatment
Last subject com-pleted: 6/08/09	≥5% weight loss from baseline Primary efficacy evaluation was conducted at Week 28 with secondary evaluation at Week 56		on NB32 were re-randomized to either NB32 or Naltrexone SR 48 mg/day and Bupropion SR 360 mg/day (NB48)	d to NB48: 123	18 to 65 years, male and female	Drug Maintenance Period: 52 Weeks Beginning Wk 28-44 Rerandomization For non-responders
NB-303 Sub-study	Ambulatory Blood Pressure Monitoring	Randomized, Double-Blind, PBO-Controlled	Same as Parent Trial NB-303 (above)	182	Eligible Subjects from the Parent NB-303 Trial	52 week double-blind assessment
NB-304 1st subject enrolled: 05/29/07 Last subject com-pleted: 6/01/09	Percent change from baseline to endpoint in body weight;; Proportion of subjects with ≥5% weight loss from baseline	Multicenter, Randomized, Double-Blind, PBO-Controlled	Placebo Naltrexone SR 32 mg/day and Bupropion SR 360 mg/day (NB32)	505/ Placebo: 170 NB32: 335	Obese or Overweight Subjects with Type 2 DM and with or without controlled hypertension and/or dyslipidemia (27-45 kg/m2); 20 to72 years, male and female	56 weeks Titration Period: 4 Weeks Drug Maintenance Period: 52 weeks

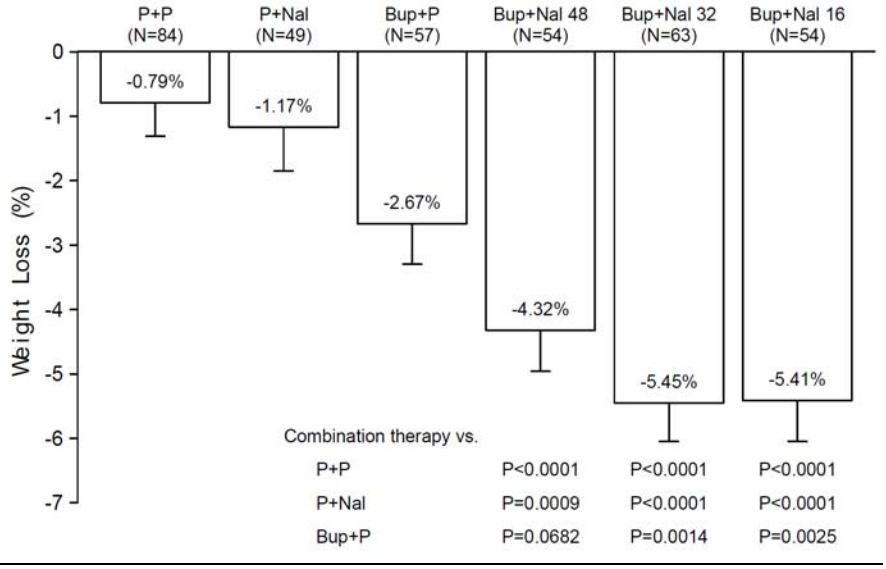
4.2 Discussion of Individual Clinical Trials

The FDA 2007 Draft Guidance for Developing Products for Weight-Management Fixed-dose Combination states "we recommend that the efficacy and safety of fixed-dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-management effects of the products. We have not defined a minimum difference in weight loss between a fixed-dose combination and its individual component products that should be achieved for the combination to be considered more efficacious than either of its components when used alone. However, a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss."

Study NB-201 was the phase 2 trial designed to satisfy the 2007 Division guideline. As demonstrated in Figure 1, subjects randomized to the three NB combination treatment groups achieved greater weight loss after 24 weeks of treatment compared with subjects randomized to the placebo and monotherapy treatment groups. There was no dose-response relationship among the 3 naltrexone dose levels studied in the NB combination treatment groups (bupropion dose

was 400 mg in each bupropion treatment group). However, as NB48 compared to the bupropion monotherapy treatment group did not reach statistical significance, significance testing of the NB32 and NB16 treatment groups was precluded under the closed testing procedure. Conducting pairwise comparisons of the 2 lower dose NB combination therapy groups to placebo and monotherapy would increase the type 1 error rate above the prespecified level of 5%. To avoid such inflation of the type 1 error, Orexigen performed pairwise comparisons of these NB dose groups, evaluated in a post-hoc manner using a Bonferroni multiple comparison procedure, which resulted in an adjusted 2-sided significance level of 0.0056 (i.e., 0.05 divided by 9, where 9 equals the total number of pairwise comparisons performed for the ITT analysis of the primary efficacy endpoint). All pairwise comparisons for the NB32 and NB16 treatment groups were statistically significant at the adjusted alpha level of 0.0056 (largest *P*-value .0025). The proportion of patients who achieved 5% or greater weight loss was approximately 2-fold greater for the Bup 400mg+Nal 32 mg combination treatment group (51%) compared to the Bup 400mg monotherapy treatment group (26%).

Figure 1: Mean (±SE) Weight Loss at 24 Weeks, ITT Population: Cohorts 1 and 2



The results are based on data from Cohorts 1 and 2. Subjects randomized to receive P+P (BPL and NPL) in Cohorts 1 and 2 were combined. Missing values at Week 24 were imputed using a LOCF procedure. The estimated mean change from baseline (LS Mean) in each treatment group is unadjusted for baseline factors. The error bar represents the mean minus 1 standard error. P-values were determined using the two-sample t-test.
Abbreviations: BPL (or P) = bupropion-matched placebo; NPL (or P) = naltrexone-matched placebo; Bup = bupropion; Nal = naltrexone; N = total number of subjects in treatment group.

For the primary treatment period (Weeks 1-24), nausea, headache, dizziness, vomiting, insomnia, and nasopharyngitis were the most frequently reported AEs. The incidence of nausea and vomiting was higher in the NB combination treatment and naltrexone monotherapy treatment group compared to the placebo and bupropion monotherapy treatment groups. The vital signs data are consistent with modest increases in the incidence of elevations from baseline in systolic blood pressure, diastolic blood pressure, and pulse rate with bupropion treatment. Creatinine increased in the treatment arms that contained bupropion—mean change ranged from 0.10 to 0.12 mg/dL in the bupropion monotherapy, Bup+Nal 16, and Bup+ Nal 32 arms, with a smaller

increase in Bup+Nal 48 arm. The placebo and naltrexone monotherapy arms were similar in terms of creatinine change—0.04 and 0.03 mg/dL, respectively. The profile of AEs was consistent with the known effects of naltrexone and bupropion.

At the End-of-Phase 2 meeting in 10/2007, FDA accepted the Phase 2 data as sufficient to support conduct of Orexigen's Phase 3 program of naltrexone/bupropion vs placebo.

5 Review of Efficacy

5.1 Indication

Orexigen is seeking the following indication:
Contrave®, a dual pro-opiomelanocortin cell [POMC] enhancer, 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. Contrave is recommended for patients with an initial body mass index ≥30 kg/m^2 or ≥27 kg/m^2 with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension).

5.1.1 Methods

The efficacy, safety and tolerability of NB were evaluated across four Phase 3 trials in obese subjects receiving customary diet and behavioral counseling (Trials NB-301 and NB-303), in obese subjects undergoing intensive lifestyle modification counseling (Trial NB-302), and in obese subjects with type 2 diabetes (Trial NB-304). In each of these trials, the efficacy of NB was established using the FDA recommended co-primary endpoints of mean change from baseline in body weight at endpoint and the proportion of individuals who achieved a ≥5% reduction in body weight at endpoint. Although Trials NB-301, NB-302 and NB-303 enrolled a similar patient population (i.e., female and male subjects between 18 to 65 years with a body mass index (BMI) ≥ 30 and ≤ 45 kg/m^2 for subjects with uncomplicated obesity (no presence of hypertension, dyslipidemia, or type 2 diabetes), or BMI of ≥ 27 and ≤ 45 kg/m^2 for subjects with controlled hypertension and/or dyslipidemia), there were unique design elements associated with each of these trials. Of note, subjects with CVD were excluded from these trials.

All Phase 2 and 3 trials included a 4-week titration period (dose was escalated during the first 3 weeks) followed by a maintenance dosing regimen; NB-303 also included a 5-week slow titration arm (dose was escalated during the first 4 weeks).

- **Trial NB-301**: a 56-week, multicenter (34 centers, all in US), double-blind, placebo-controlled trial that investigated two daily doses of NB (naltrexone 16 mg/bupropion 360 mg [NB16] and naltrexone 32 mg/bupropion 360 mg [NB32]). Subjects were randomized to NB32 (n=583), NB16 (n=578) or placebo (n=581) in a 1:1:1 ratio. Subjects received ancillary therapy every 12 weeks consisting of diet instruction and advice on behavior

modification and exercise. At the end of the trial, subjects were randomized to either abrupt or gradual study drug discontinuation over a one week period in a blinded manner to assess for adverse events that could occur upon abrupt discontinuation of NB.

- **Trial NB-301 sub-study:** measured body composition using dual energy X-ray absorptiometry (DEXA) and a multi-slice computed tomography (CT) scan in a subset of subjects identified prior to randomization in the parent trial (124 subjects with baseline and endpoint DEXA and 58 subjects with baseline and endpoint CT) enrolled at 8 sites with the required equipment and personnel. Subjects participating at those sites could opt to participate in either DEXA and CT scan procedures or the DEXA scan procedure alone. Subjects continued through screening procedures for the NB-301 trial, and if deemed eligible for randomization, the DEXA and/or CT scans were performed prior to randomization in the NB-301 trial.

- **Trial NB-302:** a 56-week, multicenter (9 centers, all in US), double-blind, placebo-controlled trial that assessed the efficacy and safety of NB32 in a population of obese subjects undergoing an intensive behavioral modification program that included dietary instructions, prescribed exercise, and 28 closed group sessions on lifestyle modification counseling. The 28 sessions were scheduled once every week for 16 weeks (starting no later than 4 weeks post-randomization), once every 2 weeks for 12 weeks, and monthly thereafter. Subjects were randomized to NB32 (n=591) or placebo (n=202) in a 3:1 ratio.
- **Trial NB-303:** a 56-week, multicenter (36 centers, all in US), double-blind, placebo-controlled trial that was similar in design to Trial NB-301. Subjects were randomized to NB32 or placebo in a 2:1 ratio. In contrast to Trial NB-301, subjects receiving active treatment NB32 who failed to lose at least 5% of baseline body weight at Week 28 were re-randomized to either continue NB32 or increase total study drug daily dose to naltrexone SR 48 mg/bupropion SR 360 mg (NB48) per day. Subjects not re-randomized at Week 28 but who did not maintain at least 5% of baseline body weight loss during Weeks 32-44 were also re-randomized. Subjects were only re-randomized once; 123 subjects were re-randomized. Orexigen was informed that for NB-303, the primary efficacy weight loss endpoint should be at Week 28 and the weight loss endpoints at Week 56 can only be used in supportive analyses. FDA views the Week 56 results in Trial NB-303 to be exploratory in nature, and not primary or secondary endpoints. The reason is due to the differential treatment of the two randomized study arms which begins at Week 28 with the re-randomization protocol and continues through Week 44.

- **Trial NB-303 sub-study:** blood pressure was measured over a 24-hour period at baseline, and after approximately 24 and 52 weeks of therapy. Placebo (n=495); NB32 (n=1001)

- **Trial NB-304:** a multicenter (53 centers, all in US), 56-week, randomized, double-blind, placebo-controlled trial, compared the safety and efficacy of NB32 and placebo in obese subjects with type 2 diabetes mellitus and with or without controlled hypertension and/or dyslipidemia. Subjects were randomized to NB32 (n=335) or placebo (n=170) in a 2:1 ratio. The trial enrolled female and male subjects with type 2 diabetes mellitus between 18 to 70 years with a BMI ≥ 27 and ≤ 45 kg/m^2. Subjects with type 2 diabetes mellitus were eligible if they were not taking injectable diabetes medications or inhaled insulin for at least 3 months prior to randomization and these medications were not to be taken during the trial with exceptions made for short rescue periods.

Key Exclusion Criteria NB-301, NB-302, NB-303, NB-304

- Class III or IV CHF; history of MI, angina, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke
- History of seizures or predisposition to seizures (history of CVA, head trauma, febrile seizures, etc.)
- Renal or hepatic impairment (clinically significantly abnormal creatinine; AST or ALT >2.5x ULN)
- Creatinine levels >1.4 mg/dL for women, >1.5 mg/dL for men (Trial NB-304)
- Diabetes mellitus (except NB-304 which enrolled only subjects with Type 2 diabetes with HbA1c between 7-10% not on insulin)
- SBP > 140/DBP > 90 (NB-304 SBP ≥ 145/DBP ≥ 95); Anti-hypertensive meds allowed
- Opioid medication within 7 days of randomization
- Serious psychiatric illness: history of bipolar disorder, schizophrenia, psychosis, bulimia, anorexia nervosa; current serious personality disorder or severe major depressive disorder, recent (previous 6 months) suicide attempt or current active suicidal ideation, recent hospitalization due to psychiatric illness
- Concomitant medications: Any psychotropic agents (including antipsychotic, antidepressant, anxiolytic, mood stabilizer, anticonvulsant agents or agents for the treatment of Attention Deficit Disorder with the exception of short-term insomnia); any anorectic or weight loss agents; alpha-adrenergic blockers; dopamine agonists; clonidine; coumadin; theophylline; cimetidine; oral corticosteroids; cholestyramine, cholestipol, DepoProvera®; smoking cessation agents; use of opioid or opioid-like medications, including analgesics and antitussives
- Inventory of Depressive Symptomatology Subject-Rated (IDS-SR) scores ≥2 on items 5 (sadness), 6 (irritability), 7 (anxiety/tension) and 18 (suicidality), and IDS-SR total score is ≥30.

More Detailed Information on Inclusion/Exclusion Criteria and the Non-drug Ancillary Therapy for Weight Loss among the 4 Phase 3 Trials can be found in Appendix A.

5.1.2 Demographics

Orexigen's Integrated Summary of Safety (ISS) includes three Phase 2 and 3 integrated datasets: the primary placebo-controlled integrated safety analysis dataset, the overall NB exposure integrated safety analysis dataset, and the secondary placebo-controlled integrated safety analysis dataset (hereafter referred to as the Primary, Overall, and Nondiabetic datasets). These datasets include data from all randomized subjects who were administered 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 discontinued the trial.

Across the Primary Dataset, 82-85% of subjects were female, 74-79% were White, and 52-54% were between the ages of 45 to 64 years of age. Of note, only 1-2% of subjects were 65 years or older—32 subjects on placebo and 62 subjects on NB. The mean and median for baseline characteristics (i.e., height, weight, BMI) were similar across dose and treatment groups. In each dose and treatment group, subjects were evenly distributed between the four obesity classes. Of

note, approximately 23% to 25% of subjects were in the ≥40 kg/m^2 obesity class while less than 3% of subjects in each dose and treatment group were in the <30 kg/m^2 obesity class.

Table 8: Summary of Demographics: Primary Dataset

Variable	Placebo (N=1515)	NB16 (N=633)	NB32 (N=2545)	Total NB (N=3239)
Age (years)				
Mean	45	44	46	46
Subgroups, n (%):				
18-44	686 (45%)	301 (48%)	1113 (44%)	1443 (45%)
45-64	797 (53%)	326 (52%)	1376 (54%)	1734 (54%)
>=65	32 (2%)	6 (1%)	56 (2%)	62 (2%)
Gender, n (%)				
Female	1247 (82)	538 (85)	2098 (82)	2690 (83)
Ethnicity, n (%)				
Hispanic	166 (11)	74 (12)	231 (9)	306 (9)
Race				
White	1193 (79)	467 (74)	1974 (78)	2477 (77)
Black	261 (17)	137 (22)	453 (18)	614 (19)
Asian	15 (1)	4 (1)	30 (1)	34 (1)
Other	46 (3)	25 (3)	88 (3)	114 (3)
Weight (kg)				
Mean	100	99	101	100
BMI (kg/m^2)	36	36	36	36
Obesity Class, n (%)				
BMI < 30 kg/m^2	31 (2)	16 (3)	69 (3)	85 (3)
BMI ≥ 30 and < 35 kg/m^2	547 (36)	246 (39)	960 (38)	1234 (38)
BMI ≥ 35 and < 40 kg/m^2	596 (39)	228 (36)	876 (34)	1135 (35)
BMI ≥ 40 kg/m^2	341 (23)	143 (23)	640 (25)	785 (24)
Hypertension, n (%)	367 (24)	129 (20)	646 (25)	780 (24)
Diabetes, n (%)	169 (11)	0	333 (13)	333 (10)
Dyslipidemia, n (%)	801 (53)	315 (50)	1416 (56)	1753 (54)
History of Depression, n (%)	193 (13)	46 (7)	305 (12)	353 (11)
History of Anxiety, n (%)	63 (4)	22 (4)	103 (4)	126 (4)

Source: Orexigen Table ISS.P.3-1
Abbreviations: min=minimum; max=maximum; SD=standard deviation; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.
Hypertension subgroup is defined as diagnosed at baseline with hypertension or prescribed antihypertensive concomitant medication.

Demographic and other characteristics of the population were reasonably similar for the Total NB and placebo groups. Approximately 60% of subjects (61.6% for the Total NB and 60.1% for the placebo groups) had complicated obesity, approximately half had dyslipidemia (54.1% Total NB, 52.9% placebo), approximately one third had impaired fasting glucose (32.3% and 32.4% respectively), and approximately a quarter had hypertension (24.1 % and 24.2% respectively). A minority of subjects in the Total NB and placebo groups had diabetes (10.3% and 11.2% respectively); all were in the placebo or NB32 groups from Trial NB-304. A small percentage of subjects had a history of depression (10.9% Total NB, 12.7% placebo) or anxiety (3.9% and

4.2% respectively), and mean IDS-SR score at baseline was 6.81 (range 0 to 41) and 6.67 (range 0 to 39), respectively. Most subjects were between 31 and 64 years of age (86.7% and 86.1% for NB and placebo treatment groups, respectively), only 3.8% of subjects in both the NB and placebo groups were between the ages of 18 and 25 years of age and only ~2% of subjects were 65 years or older. The small number of individuals 65+ years of age limits the assessment of AEs that would be more prevalent in an older population, such as CV disease and hypertension.

Although CVD was an exclusion criterion for these trials (specifically, Class III or IV congestive heart failure; history of myocardial infarction, angina pectoris, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke), there were a few subjects with a past medical history of myocardial infarction, stroke or other established CVD in the clinical development program. As shown in the table below, there were 5 (0.3%) subjects with past medical history events in the placebo group and 9 (0.3%) subjects with past medical history events in the NB group of myocardial infarction.

Table 9: Medical History, by Preferred Term, in Subjects with Ischemic Medical History*

System Organ Class **Preferred Term**	**PLB** **N=1515** **n (%)**	**NB** **N=3239** **n (%)**
Cardiac Disorders	**17 (1.1%)**	**30 (0.9%)**
Coronary artery disease	8 (0.5%)	16 (0.5%)
Myocardial infarction	5 (0.3%)	9 (0.3%)
Angina pectoris	4 (0.3%)	5 (0.2%)
Bundle branch block left	0	2 (0.1%)
Cardiomyopathy	0	2 (0.1%)
Arteriosclerosis coronary artery	0	1 (0.0%)
Myocardial ischaemia	1 (0.1%)	1 (0.0%)
Cardiovascular disorder	1 (0.1%)	0
Atrial fibrillation	0	1 (0.0%)
Cardiac hypertrophy	0	1 (0.0%)
Palpitations	0	1 (0.0%)
Tachycardia	1 (0.1%)	1 (0.0%)
Tricuspid valve incompetence	0	1 (0.0%)
Cardiomegaly	1 (0.1%)	0
Coronary ostial stenosis	1 (0.1%)	0
Mitral valve incompetence	1 (0.1%)	0
Mitral valve prolapse	1 (0.1%)	0
Sinus arrhythmia	1 (0.1%)	0
Nervous System Disorders	**3 (0.2%)**	**4 (0.1%)**
Transient ischaemic attack	3 (0.2%)	3 (0.1%)
Cerebrovascular accident	0	2 (0.1%)
Surgical and medical procedures	**4 (0.3%)**	**9 (0.3%)**
Coronary artery bypass	2 (0.1%)	4 (0.1%)
Angioplasty	1 (0.1%)	2 (0.1%)
Coronary arterial stent insertion	1 (0.1%)	2 (0.1%)
Vascular bypass graft	1 (0.1%)	1 (0.0%)

Notes: Medical history diagnoses were coded using MedDRA version 9.1.

Subjects with multiple medical history diagnoses were counted once within each MedDRA SOC level. However, Preferred Term events are counted, not subjects, so one subject may have experienced more than one preferred term event
Source: Excerpt from Orexigen Table 26Jul2010 - 5.1.4

Reviewer comment: The limitations of the NB database include the small number of male subjects (17% in Total NB group); limited ethnic/racial diversity (19% Black, 9% Latinos, 1% Asian); and limited baseline co-morbidities [depression (11% NB, 13% Pbo), anxiety (4% in both), diabetes (10% NB, 11% Pbo), hypertension (24% in both), 0.5% with coronary artery disease, 0.3% with previous myocardial infarction, and 0.1% NB and 0% placebo with prior CVA.]

Concomitant Medications

The most common (>20% incidence in any group) classes of concomitant medications were ACE inhibitors; angiotensin II antagonists; anilides; biguanides; HMG CoA reductase inhibitors; multivitamins; platelet aggregation inhibitors excluding heparin; propionic acid derivatives (NSAIDS); sulfonamides, urea derivatives; thiazides; and thiazolidinediones.

Not surprisingly, the prevalence of antihypertensive medication use (classes of ACE inhibitors, angiotensin II antagonists, and thiazides) and medication to treat heart disease (beta blocking agents, dihydropyridine derivatives, and platelet aggregation inhibitors) was much higher in the Diabetics Dataset (NB-304) compared with the Nondiabetic Dataset (Trials NB-301, 301, and 303). Beta blocker concomitant medication was an exclusion criterion in the original NB-304 protocol that was removed in a protocol amendment. In the Primary dataset, use of beta-blockers as a concomitant medication occurred in 4.4% of subjects assigned to placebo and 4.8% of subjects assigned to NB.

In the nondiabetic dataset (Trials NB-301, 302, and 303), 10% of placebo-treated subjects and 11% of NB32-treated subjects were on concomitant statin therapy. In the diabetic dataset (Trial NB-304), 46% of placebo-treated subjects and 50% of NB32-treated subjects were on concomitant statin therapy. All trials excluded antidepressant use as an entry criterion and prohibited use during the trial.

Table 10: Summary of Concomitant Medication Taken by ≥10% of Subjects In Any Group: Comparison of Diabetic and Nondiabetic Datasets, Safety Analysis

	Nondiabetic Dataset		**Diabetic Dataset**	
Concomitant Medication Class	**Placebo (N=1346) n (%)**	**NB32 (N=2212) n (%)**	**Placebo (N=169) n (%)**	**NB32 (N=333) n (%)**
Subjects ≥1 concomitant medication	**1199 (89.1)**	**1985 (89.7)**	**168 (99.4)**	**328 (98.5)**
ACE Inhibitors, Plain	99 (7.4)	179 (8.1)	59 (34.9)	142 (42.6)
Angiotensin II Antagonists, Plain	78 (5.8)	116 (5.2)	36 (21.3)	75 (22.5)
Anilides	402 (29.9)	672 (30.4)	45 (26.6)	70 (21.0)
Beta Blocking Agents, Selective	**<5%**	**<5%**	**23 (13.6)**	**38 (11.4)**
Biguanides	<5%	<5%	137 (81.1)	267 (80.2)
Calcium	127 (9.4)	239 (10.8)	18 (10.7)	31 (9.3)

Concomitant Medication Class	Nondiabetic Dataset		Diabetic Dataset	
	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB32 (N=333) n (%)
Dihydropyridine Derivatives	<5%	<5%	15 (8.9)	40 (12.0)
Glucocorticoids	139 (10.3)	177 (8.0)	13 (7.7)	28 (8.4)
HMG CoA Reductase Inhibitors	**135 (10.0)**	**243 (11.0)**	**78 (46.2)**	**165 (49.5)**
Multivitamins, Plain	341 (25.3)	591 (26.7)	47 (27.8)	73 (21.9)
Other Antihistamines for Systemic Use	170 (12.6)	266 (12.0)	19 (11.2)	23 (6.9)
Other Lipid Modifying Agents	**123 (9.1)**	**225 (10.2)**	**32 (18.9)**	**50 (15.0)**
Other Oral Blood Glucose Lowering Drugs*	**2 (0.1)**	**0**	**26 (15.4)**	**31 (9.3)**
Platelet Aggregation Inhibitors Excluding Heparin	116 (8.6)	225 (10.2)	63 (37.3)	110 (33.0)
Progestogens and Estrogens, Fixed Combinations	155 (11.5)	242 (10.9)	3 (1.8)	2 (0.6)
Propionic Acid Derivatives	534 (39.7)	903 (40.8)	57 (33.7)	93 (27.9)
Proton Pump Inhibitors	142 (10.5)	254 (11.5)	25 (14.8)	59 (17.7)
Sulfonamides, Urea Derivatives	0	0	92 (54.4)	163 (48.9)
Thiazides, Plain	146 (10.8)	235 (10.6)	41 (24.3)	78 (23.4)
Thiazolidinediones	0	0	54 (32.0)	107 (32.1)
Thyroid Hormones	124 (9.2)	194 (8.8)	21 (12.4)	30 (9.0)
Unspecified Herbal	83 (6.2)	177 (8.0)	25 (14.8)	29 (8.7)

Data Source: Orexigen Table ISS.S.4-1 and ISS.D.4-1.
Concomitant medications coded using WHO Drug Dictionary version 01DEC2006. Medications were classified according to the highest level term of the Anatomical Therapeutic Chemical classifications.
*Includes avandaryl, metformin w/sitagliptin, nateglinide, repaglinide, and sitagliptin.
Abbreviations: ACE=angiotensin-converting enzyme; HMG CoA=3-hydroxy-3-methylglutaryl-coenzyme A

5.1.3 Subject Disposition

Screen failure information was collected for each of the five trials included in the Primary Dataset (NB-201, NB-301, NB-302, NB-303, and NB-304), and is summarized in the table below. Overall for the five trials, a total of 8472 subjects were screened, of whom 3644 (43%) failed screening and were not enrolled. Screen failure rates by trial ranged from 25% (Trial NB-201) to 69% (Trial NB-304). The most frequent reasons for screen failure were laboratory abnormalities and vital signs abnormalities. Trial NB-304 had the highest screen failure rate in part due to the difficulty in meeting the HbA1c inclusion criterion.

Reviewer comment: Forty-three percent of subjects failed screening and ~50% of the reasons for screen failure were lab and vital sign abnormalities-- this limits the applicability of the trial findings to the general population.

Table 11: Summary of Screen Failures by Trial

	NB-201	NB-301	NB-302	NB-303	NB-304
Total # of Subjects Screened	389 (100.0%)	2929 (100.0%)	1292 (100.0%)	2237 (100.0%)	1625 (100.0%)

	NB-201	NB-301	NB-302	NB-303	NB-304
Total # of Subjects Randomized	292 (75.1%)	1742 (59.5%)	793 (61.4%)	1496 (66.9%)	505 (31.1%)
Total # of Screen failures	97 (24.9%)	1187 (40.5%)	499 (38.6%)	741 (33.1%)	1120 (68.9%)
Reasons for Screen Failures					
Lab Abnormality	44 (45.4%)	270 (22.7%)	107 (21.4%)	195 (26.3%)	646 (57.7%)
Vital Sign Abnormality	8 (8.2%)	239 (20.1%)	122 (24.4%)	112 (15.1%)	60 (5.4%)
HAD >= 11 (Hospital Anxiety and Depression Scales)	8 (8.2%)	---	---	---	---
IDS-SR (Inventory of Depressive Symptoms - Subject Rated)	---	36 (3.0%)	23 (4.6%)	28 (3.8%)	18 (1.6%)
BMI < 27	---	6 (0.5%)	---	4 (0.5%)	5 (0.4%)
BMI < 30	1 (1.0%)	26 (2.2%)	9 (1.8%)	15 (2.0%)	---
BMI > 40	1 (1.0%)	---	---	---	---
BMI > 45	---	48 (4.0%)	18 (3.6%)	25 (3.4%)	25 (2.2%)
ECG Abnormality	3 (3.1%)	29 (2.4%)	31 (6.2%)	20 (2.7%)	12 (1.1%)
Failed Bipolar Question or Presence of Bipolar Disorder	---	2 (0.2%)	1 (0.2%)	6 (0.8%)	2 (0.2%)
Concomitant Medication	---	59 (5.0%)	20 (4.0%)	37 (5.0%)	73 (6.5%)
Lost to Follow Up	9 (9.3%)	167 (14.1%)	28 (5.6%)	82 (11.1%)	51 (4.6%)
Withdrew Consent	7 (7.2%)	148 (12.5%)	79 (15.8%)	126 (17.0%)	58 (5.2%)
Reason Not Specified	---	7 (0.6%)	2 (0.4%)	6 (0.8%)	58 (5.2%)
Did not meet entrance criteria	12 (12.4%)	150 (12.6%)	61 (12.2%)	91 (12.3%)	160 (14.3%)
(A lifetime history of serious psychiatric illness, including lifetime history of...)	---	2 (0.2%)	---	1 (0.1%)	---
(Current serious psychiatric condition)	2 (2.1%)	7 (0.6%)	---	1 (0.1%)	1 (0.1%)
(A response to Bipolar Disorder questions indicating the presence of Bipolar Diso...)	7 (7.2%)	2 (0.2%)	---	---	1 (0.1%)
(In need of medications for the treatment of a psychiatric disorder (with the exc...)	---	2 (0.2%)	1 (0.2%)	---	---
(History of seizure disorder or	1 (1.0%)	8 (0.7%)	4 (0.8%)	8 (1.1%)	3 (0.3%)

	NB-201	NB-301	NB-302	NB-303	NB-304
predisposition to seizures)					
(Normotensive (systolic <= 140; diastolic <= 90). Anti-hypertensive meds allowed...)	2 (2.1%)	9 (0.8%)	2 (0.4%)	4 (0.5%)	4 (0.4%)*
(Negative urine drug screen)	---	15 (1.3%)	---	7 (0.9%)	3 (0.3%)
(HbA1c between 7 and 10%, fasting glucose <270mg/dl, fasting triglycerides <400mg...)	---	---	---	---	12 (1.1%)
The percentages for total number of subjects screened, total number of subjects randomized, and total number of screen failures are based on the total number of subjects screened for each trial. The percentages for the reasons for screen failures are based on the total number of screen failures. A screen failure may have more than one reason recorded for not being accepted into the trial. *INC #5 (Systolic (<145); diastolic (<95). Anti-hypertensive meds are allowed with the ex...)					

Approximately 51-55% of subjects in the NB and the placebo groups completed the study treatment with the notable exception of the NB48 group where only 40% completed treatment due to a higher rate of 'lost to follow-up' and 'withdrew consent'. The Total NB group had a higher percentage of Adverse Events than the placebo group (22.9% vs. 12.0%, respectively), but a lower percentage of withdrew consent (8.6% vs. 12.7%, respectively), lost to follow up (8.0% vs. 9.6%, respectively), and discontinued treatment due to insufficient weight loss (1.7% vs. 6.1%, respectively). A summary of disposition data are presented in the following table.

Table 12: Summary of Disposition: Primary Dataset, Safety Analysis Set

	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	NB48 (N=61) n (%)	Total NB (N=3239) n (%)
Completed Treatment	828 (54.7)	322 (50.9)	1401 (55.0)	24 (39.3)	1747 (53.9)
Discontinued Treatment	687 (45.3)	311 (49.1)	1144 (45.0)	37 (60.7)	1492 (46.1)
Reason for discontinuing treatment					
Adverse event	182 (12.0)	129 (20.4)	604 (23.7)	9 (14.8)	742 (22.9)
Withdrew consent	192 (12.7)	67 (10.6)	202 (7.9)	9 (14.8)	278 (8.6)
Lost to follow up	145 (9.6)	77 (12.2)	166 (6.5)	15 (24.6)	258 (8.0)
Insufficient weight loss	92 (6.1)	14 (2.2)	40 (1.6)	0	54 (1.7)
Drug non-compliance	28 (1.8)	8 (1.3)	48 (1.9)	0	56 (1.7)
Failure to comply with protocol requirements	20 (1.3)	7 (1.1)	37 (1.5)	2 (3.3)	46 (1.4)
Subject moved	16 (1.1)	3 (0.5)	23 (0.9)	1 (1.6)	27 (0.8)
Subject became pregnant	4 (0.3)	2 (0.3)	12 (0.5)	0	14 (0.4)
Other primary reason not listed	7 (0.5)	1 (0.2)	8 (0.3)	0	9 (0.3)
Enrolled, however, did not meet selection criteria	1 (<0.1)	3 (0.5)	3 (0.1)	1 (1.6)	7 (0.2)
Death	0	0	1 (<0.1)	0	1 (<0.1)

	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	NB48 (N=61) n (%)	Total NB (N=3239) n (%)
Data Source: Table ISS.P.2-1.1.					

Subject Disposition Over Time
In the NB groups, approximately half of subjects who discontinued treatment did so by Week 8, while in the placebo group, approximately half of subjects who discontinued treatment did so by Week 12.

5.1.4 Analysis of Primary Endpoint(s)

The co-primary efficacy endpoints for the four Phase 3 trials were:

- The percent change from baseline in body weight at Week 56 (Last Observation Carried Forward [LOCF]) for trials NB-301, NB-302, and NB-304 and at Week 28 (LOCF) for trial NB-303.
- The proportion of subjects who achieved ≥5% decrease from baseline body weight at Week 56 (LOCF) for trials NB-301, NB-302, and NB-304 and at Week 28 (LOCF) for trial NB-303.

In 2007 the Division issued a draft guidance entitled Developing Products for Weight Management. The guidance stipulates that a drug will be considered effective if at least one of the following criteria is satisfied after one year of treatment:

1) 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

or

2) 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

Efficacy analyses described were conducted on the full analysis set or the completers analysis set. The full analysis set (a modification of the intent-to-treat principle) included all randomized subjects who had a baseline measurement and at least one postbaseline measurement while on study drug (i.e., active treatment or placebo).

Baseline was defined as the last non-missing measurement before, or at the time of, randomization. Endpoint was defined for the LOCF analysis as the last non-missing postbaseline measurement while on study drug. Efficacy assessments performed within 1 day after the last dose date were considered valid. Treatment effects were evaluated using a two-sided significance level of 0.05. In addition to the completers analyses, other sensitivity analyses were conducted in the full analysis set using a repeated measures mixed effects model; in the ITT analysis set using the last available data in the double-blind treatment phase and using a repeated measures mixed

effects model; and in the all randomized analysis set subjects imputing the baseline value for subjects who discontinued prior to Week 56 (BOCF) and using weight regain imputation methods.

Primary Efficacy Results:

In all four Phase 3 trials, NB32 (and NB16 in trial NB-301) 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.

- The difference in mean weight loss between NB32 and placebo-treated groups was 4.2% (range: 3.3 to 4.8%).
  - *Non-diabetic groups:* The difference in mean weight loss between NB32 and placebo-treated groups was 4.5% (range: 4.2 to 4.8%).
  - *Diabetic groups:* The difference in mean weight loss between NB32 and placebo-treated groups was 3.3%.
- The difference in mean weight loss between NB16 and placebo-treated groups was 3.7%.

However, this does not meet the first criteria set out in the 2007 draft guidance that stipulates that after one year of treatment 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.

In all four Phase 3 trials there was a statistically significant ($p<0.001$) greater proportion of subjects treated with NB32 (and NB16 in Trial NB-301) who achieved ≥5% weight loss from baseline compared with the placebo group.

Table 13: Proportion of Subjects who Achieved ≥5% Weight Loss from Baseline, LOCF

	Treatment group	Baseline mean wt (kg)	Number (%) of 5% responders	Odds ratio vs placebo (95% CI)
NB-301 Wk 56	Placebo	99	84 (16.4%)	--
	NB16	100	186 (39.5%)	3.4 (2.5, 4.6)
	NB32	100	226 (48.0%)	4.9 (3.6, 6.6)
NB-302 Wk 56	Placebo	102	82 (42.5%)	--
	NB32	101	320 (66.4%)	2.9 (2.0, 4.1)
NB-303 Wk 28	Placebo	99	80 (17.5%)	--
	NB32	101	459 (55.6%)	6.6 (5.0, 8.8)
NB-304 Wk 56	Placebo	105	30 (18.9%)	--
	NB32	106	118 (44.5%)	3.4 (2.2, 5.5)

With the exception of Trial NB-302 which employed a more intensive behavioral/lifestyle modification program, the proportion of subjects who lost greater than or equal to 5 percent of baseline body weight in the active-product group was at least 35 percent, was at least double the proportion in the placebo-treated group, and the difference between groups was statistically significant. This meets the FDA's second criteria for efficacy.

Other efficacy comments on specific trials:

- Trial NB-301: Only Trial NB-301 included a lower dose, NB16. The NB16 dose was superior to placebo; however, the NB32 dose demonstrated greater efficacy (LS mean difference from placebo, -4.81%) compared with NB16 (-3.67%) (p=0.008). In addition, there was a greater proportion of subjects achieving 5% or greater weight loss on NB32 (48.0%) compared with NB16 (39.5%) (p=0.010)

- Trial NB-302: There was greater mean weight loss from baseline in patients treated with NB32 in the NB-302 trial (-9.3%) compared to the other three studies (-6.4% to -5.0%) at Week 56, likely due to the background intensive behavioral modification counseling employed in that study. Substantial mean weight loss of -5.1% was also observed for the placebo group, which was greater than the placebo effects observed in the other three studies (-1.8% to -1.2%). In fact, the -5.1% mean weight loss achieved in the placebo group was similar to the weight loss achieved by the NB16 group in Trial NB-301 and the NB32 group in the trial in patients with type 2 diabetes, NB-304 (-5.0%). In addition, there was a greater proportion of NB32 subjects who achieved ≥5% weight loss from baseline (66.4%) compared to the other three studies at Week 56. The placebo group also had a high proportion of subjects who achieved ≥5% weight loss from baseline (42.5%) compared to the other three studies (16.4% to 18.9%).

- Trial NB-304: In obese subjects with type 2 diabetes mellitus (Study NB-304) results were less pronounced than those observed in NB-301 and NB-303. This was not unexpected as obese patients with type 2 diabetes mellitus tend to lose less weight compared to obese non-diabetic patients. The difference from placebo in percent change from baseline was only -3.3 and the proportion of subjects achieving 5% or greater weight loss was only 44.5% which is lower than what was observed in Trial NB-301 and NB-303.

Table 14: 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		

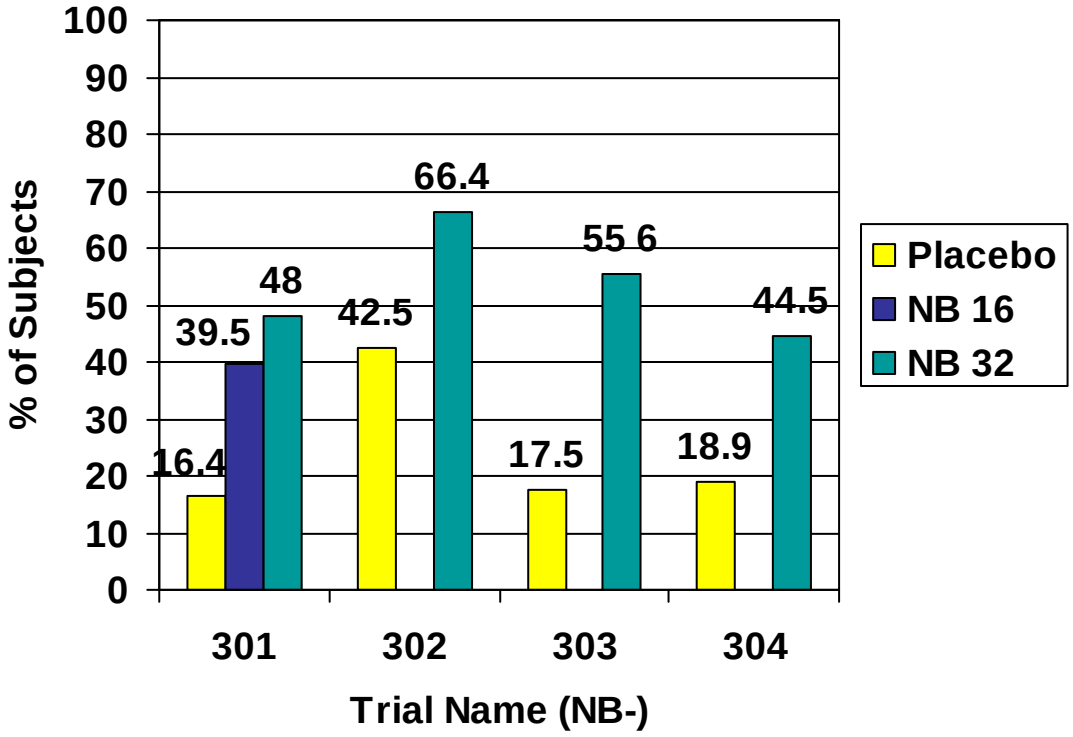
Trial NB-302: Week 52 was primary endpoint (intensive lifestyle intervention)	**NB32**	**placebo**	**Total**
1. Randomized	591	202	793
Completed 52 weeks	342 (57.9%)	118 (58.4%)	460 (58.0%)
Withdrawn before 52 wks	249 (42.1%)	84 (41.6%)	333 (42.0%)
FAS population	**482**	**193**	**675**
2. Baseline mean in kg	100.7 (15.4)	101.9 (15.0)	
3. % change from baseline, LS Mean (SE)	-9.3 (0.4)	-5.1 (0.6)	
Difference from placebo, LS Mean (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, LS Mean (SE)	-6.5 (0.2)	-1.9 (0.3)	
Difference from placebo, LS Mean (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, LS Mean (SE)	-5.0 (0.3)	-1.8 (0.4)	
Difference from placebo, LS Mean (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.

Figure 2: Percentage of Subjects with ≥ 5% Decrease from Baseline to Endpoint (LOCF)



Notes: (1) Endpoint for Trial NB-301, -302, and -304 is at Week 56; Endpoint for Trial NB-303 is Week 28. (2)The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. (3) Results are based on last-observation-carried-forward (LOCF) method while on study drug.

5.1.5 Analysis of Secondary Endpoints(s)

Analyses of these endpoints were conducted at Week 56 for Trials NB-301, NB-302 and NB-304, and at Week 28 for NB-303. Secondary endpoints included the following:

- Subjects who achieved ≥10% decrease from baseline in body weight
- Waist circumference change from baseline to endpoint
- Lipid parameters (HDL, LDL, triglycerides) change from baseline to endpoint
- Glucose and insulin parameters change from baseline to endpoint
- Glycemic control (NB-304 only) – as measured by percent change from baseline in hemoglobin A1c (HbA1c) and proportion of subjects with HbA1c <6.5%, with HbA1c <7.0%, needing rescue medications, needing change in doses of oral hypoglycemic agents, discontinued due to poor glycemic control

- High-sensitivity C reactive protein (hs-CRP)
- Systolic and diastolic blood pressure
- Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire
- Control of Eating (COE) questionnaire
- Food Craving Inventory (FCI) questionnaire
- Inventory of Depressive Symptomatology Subject-Rated (IDS-SR) questionnaire

5.1.5.1 Proportion of Subjects with ≥10% Weight Loss from Baseline

In the four Phase 3 trials, NB (16 and 32) treatment resulted in a statistically significant greater proportion of subjects achieving ≥10% weight loss compared with placebo.

Table 15: Proportion of Subjects with ≥ 5%, ≥ 10%, and ≥ 15% Decrease from Baseline after Treatment with NB32 (Full Analysis Set, LOCF)

Variable	NB-301			NB-302		NB-303		NB-304	
Duration	56 weeks			56 weeks		28 weeks		56 weeks	
	Placebo	NB16	NB32	Placebo	NB32	Placebo	NB32	Placebo	NB32
N	511	471	471	193	482	456	825	159	265
≥ 5% Weight Loss	16.4%	39.5%*	48.0%*	42.5%	66.4%*	17.5%	55.6%*	18.9%	44.5%*
≥ 10% Weight Loss	7.4%	20.2%*	24.6%*	20.2%	41.5%*	7.0%	27.3%*	5.7%	18.5%*
≥ 15% Weight Loss	2.0%	8.7%*	11.9%*	10.9%	29.1%*	1.8%	10.2%*	2.5%	4.5%†

Source: Table NB-301 Tables: CSR 14.2-18A, 14.2-30A, 17.1-1A; NB-302 CSR Tables: 14.2-17, 14.2-28A, 17.1-1; NB-303 CSR Tables: 14.2-32A, 17.1-2, 14.2-53; NB-304 CSR Tables: 14.2-20A, 14.2-47A, 17.1-9A.
Abbreviations: NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg
* p<0.001
† p=NS
The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on last-observation-carried forward (LOCF) method while on study drug.

Another analysis looks at change in weight across four weight loss categories.

Table 16: Proportion of Patients who Achieved Specific Categories of Body Weight Change (Full Analysis Set, LOCF)

	Placebo	NB32	Difference between NB32 and Placebo
N	1319	2043	
No Change/gain	573 (43.4%)	355 (17.4%)	-26.0%
>0 to < 5% Weight Loss	472 (35.8%)	603 (29.5%)	-6.3%
≥ 5 to < 10% Weight Loss	162 (12.3%)	485 (23.7%)	+11.4%
≥ 10% Weight Loss	112 (8.5%)	600 (29.4%)	+20.9%

Source: Derived from Orexigen Figure 27Sep2010 – 1.2.2
The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on last-observation-carried forward (LOCF) method while on study drug.
Abbreviations: NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg

5.1.5.2 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.

Table 17: Waist Circumference Change from Baseline to Endpoint

Variable	**NB-301**			**NB-302**		**NB-303**		**NB-304**	
Duration	56 weeks			56 weeks		28 weeks		56 weeks	
	Placebo	NB16	NB32	Placebo	NB32	Placebo	NB32	Placebo	NB32
N	348	342	356	141	391	315	622	124	208
Change in waist circumference from baseline (cm), LS Mean	-2.5	-5.0	-6.2	-6.8	-10.0	-2.7	-6.2	-2.9	-5.0
Difference from placebo, LS Mean		-2.6	-3.8		-3.2		-3.4		-2.1
p-value		<0.001	<0.001		<0.001		<0.001		0.006

Source: Table NB-301: Table 14.2-33; NB-302: Table 14.2-30; NB-303: Table 14.2-59; NB-304: Table 14.2-52
Abbreviations: NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg
The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on last-observation-carried forward (LOCF) method while on study drug.

5.1.5.3 Lipid parameters (HDL, LDL, triglycerides) change from baseline to endpoint

HDL: Changes in fasting HDL cholesterol were consistent across the four trials in that the increase in HDL levels seen with NB (16 and 32 mg) were greater than placebo and reached statistical significance in all 4 trials. The LS Mean treatment differences from placebo ranged from 2.6 to 3.5 mg/dL.

Triglycerides: The reduction in percentage from baseline was consistent across the four trials in that the decrease in triglycerides levels with NB16 and NB32 was greater than placebo and reached statistical significance in all four trials. The decrease in TG was 8% in the NB16 group and ranged from 7 to 17% in the NB32 groups. 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 were not statistically different from placebo.

Table 18: Lipid Parameters (HDL, LDL, triglycerides) Change from Baseline to Endpoint

Variable	NB-301			NB-302		NB-303		NB-304	
Duration	56 weeks			56 weeks		28 weeks		56 weeks	
	Placebo	NB16	NB32	Pbo	NB32	Pbo	NB32	Pbo	NB32
N	345	333	359	144	392	308	625	135	222
HDL-C change from baseline (mg/dL), LS Means	-0.1	3.4	3.4	0.9	4.1	-1.4	1.2	-0.3	3.0
Difference from placebo, LS Mean		3.4	3.5		3.2		2.6		3.3
p-value		<0.001	<0.001		<0.001		<0.001		<0.001
TG change* from baseline (mg/dL), LS % Change	-3.1%	-8.0%	-12.7%	-8.5%	-16.6%	-1.4%	-7.3%	-0.8%	-11.2%
Difference from placebo		-4.9%	-9.6%		-8.1%		-5.9%		-10.4%
p-value		0.046	<0.001		0.004		0.007		0.007
LDL-C change from baseline (mg/dL), LS Means	-3.3	-3.7	-4.4	8.1	5.4	0	-4.4	0	-1.4
Difference from placebo, LS Mean		-0.4	-1.1		-2.7		-4.4		-1.4
p-value		0.811	0.484		0.245		0.004		0.641

Source: Table NB-301 14.2-38, 14.2-34, 14.2-48; NB-302: Tables 14.2-32, 14.2-38, 14.2-52; Table NB-303:14.2-65, 14.2-61, 14.2-79; NB-304: Tables 14.2-37, 14.2-41, 14.2-57

* For triglycerides, examination of the distribution of baseline values indicated a skewed distribution such that the assumptions underlying regression analyses were not met. The data on fasting triglycerides levels were analyzed by the sponsor using a log 10 transformation of data.

Abbreviations: NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg

The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on last-observation-carried forward (LOCF) method while on study drug.

5.1.5.4 Glucose and insulin parameters change from baseline to endpoint in the three Phase 3 trials in obese subjects without diabetes mellitus (NB-301, NB-302, and NB-303)

- Improvements in fasting glucose from baseline were greater for the NB group compared with placebo but were only statistically significant for the NB32 dose in Trial NB-301. In NB-301, the LS mean difference from placebo was -1.9 mg/dL.
- Improvements in fasting insulin from baseline geometric mean were greater for the NB group compared with placebo. The analyses showed statistically significant differences for NB32 compared with placebo for Trials NB-301 and NB-302 only.
- Improvements in HOMA-IR (the homeostasis model assessment of insulin resistance) were greater for the NB group compared with placebo. The analyses showed statistically significant differences for NB compared with placebo for Trials NB-301 and NB-302 only.

5.1.5.5 Glycemic control (NB-304 only) – as measured by percent change from baseline in hemoglobin A1c (HbA1c) and proportion of subjects with HbA1c <6.5%, with HbA1c <7.0%, needing rescue medications, needing change in doses of oral hypoglycemic agents, discontinued due to poor glycemic control

- Percent change from baseline in HbA1c: Baseline mean HbA1c values were similar between the treatment groups (7.97% NB32 and 7.99% placebo). 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).
- Proportion of subjects with HbA1c <6.5% and with HbA1c <7.0%: Hypothesis testing was concluded prior to these analyses, so these findings are considered post-hoc and exploratory. However the proportion of subjects with HbA1c below 7% at endpoint in the NB32 group was numerically greater than placebo (44.1% vs. 26.3%) and the proportion of subjects with HbA1c below 6.5% at endpoint in the NB32 group was numerically greater than placebo (20.7% NB32 vs. 10.2% placebo).
- The proportion of subjects requiring rescue medications for poor hyperglycemic control in the NB32 group was lower than placebo treatment (22.3% NB32 vs. 35.2% placebo).
- There were few subjects in each group with either dose reductions in oral hypoglycemic medication (1.3% placebo, 1.9% NB32), dose increases (1.3% placebo; 3.0% NB32), or who discontinued investigational therapy due to poor glycemic control (1.9% placebo; 0.0% NB32).

5.1.5.6 High-sensitivity C reactive protein (hs-CRP)

In all four trials, for both placebo and NB groups, there was a decrease in hs-CRP (percent change geometric mean) from baseline to endpoint. Subjects in the NB treatment groups showed a greater percentage decrease from baseline in hs-CRP compared with placebo--this was statistically different from placebo in Trial NB-301 only.

Table 19: hs-CRP Levels (mg/L), Percent Change from Baseline to Endpoint by Phase 3 Study Using Log-transformed Data (Full Analysis Set)

Variable	NB-301			NB-302		NB-303		NB-304	
Duration	56 weeks			56 weeks		28 weeks		56 weeks	
	Placebo	NB16	NB32	Placebo	NB32	Placebo	NB32	Placebo	NB32
N	340	331	353	143	386	304	607	119	202
Baseline geometric mean	3.57	3.89	3.83	4.20	3.86	3.68	3.88	3.25	3.55
% change geometric mean	-14.5	-27.0	-27.8	-25.2	-30.9	-1.5	-10.8	-9.2	-19.6
LS % change	-16.7	-28.0	-29.0	-16.9	-25.8	-1.1	-9.4	-13.3	-20.9
Difference from placebo		-11.3%	-12.3%		-8.9%		-8.3%		-7.6%
p-value		0.016	0.008		0.165		0.091		0.312

Source: Table NB-301: Table 14.2-44; NB-302: Table 14.2-46; NB-303: Table 14.2-75; NB-304: Table 14.2-55
Abbreviations: NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg
The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on last-observation-carried forward (LOCF) method while on study drug.

5.1.5.7 Systolic and diastolic blood pressure

This is a key safety endpoint and is discussed in detail in *Section 6.3.4.1. Blood Pressure and Pulse*.

5.1.5.8 Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire

The Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire[13] is a 31-item, self-report questionnaire designed to assess the effect of obesity on quality of life. This scale is organized into 5 subscales: physical function (11 items), self-esteem (7 items), sexual life (4 items), public distress (5 items), and work (4 items). All items were rated using a 5 point scale. In all four Phase 3 trials, the total score and the subscale scores were transformed into a 0 (worst) to 100 (best) scale.

The results of the IWQOL- Lite questionnaire total score (see table below) 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. In Trial NB-304, the difference in the IWQOL-Lite total score was not statistically significant.

13 Kolotkin RL, Crosby RD, Kosloski KD, William G R: Development of a brief measure to assess quality of life in obesity. Obes Res 2001; 9: 102-111.

Table 20: IWQOL-Lite Total Score, Change from Baseline to Endpoint Full Analysis Set, Double-Blind Treatment Phase by Trial

Trial	Treatment Group	n	Baseline Mean (SD)	Change from Baseline LS Mean (SE)	LS Mean Difference from Placebo (SE)	95% CI	p-value
NB-301	Placebo	468	71.8 (17.2)	8.0 (0.51)			
	NB16	422	70.7 (17.0)	11.7 (0.5)	3.1 (0.7)	(1.7, 4.5)	<0.001
	NB32	417	70.3 (16.5)	12.7 (0.5)	4.1 (0.7)	(2.7, 5.6)	<0.001
NB-302	Placebo	179	73.9 (15.7)	10.2 (0.9)			
	NB32	448	71.9 (15.4)	13.4 (0.6)	3.2 (1.0)	(1.3, 5.1)	0.001
NB-303 *Week 28 Endpoint*	Placebo	317	72.9 (15.7)	6.2 (0.6)			
	NB32	628	72.0 (17.4)	9.9 (0.4)	3.8 (0.7)	(2.5, 5.1)	<0.001
NB-304	Placebo	153	73.5 (16.9)	7.9 (0.9)			
	NB32	241	73.2 (17.2)	9.3 (0.7)	1.4 (1.1)	(-0.8, 3.5)	0.208
Source: Orexigen Table ISE.P3.8-1							

An algorithm for determining whether changes in IWQOL-Lite scores are meaningful has been described by Crosby and colleagues[14,15]. The authors state that a meaningful change in HRQoL (health related quality of life) can be determined using an integrated method that (1) combines information from anchor-based and distribution-based methods, (2) reconciles discrepancies between these two methods, and (3) adjusts for baseline severity and regression to the mean. Using this integrated method, an improvement of 7.7 to 12 points (depending on baseline severity) on IWQOL-Lite total score is considered meaningful.

Thus, while some of the naltrexone/bupropion trials showed a statistically significant difference in the total score associated with NB treatment compared with placebo, none of the trials showed a clinically meaningful difference between NB and placebo in the IWQOL-Lite total score.

In addition, this division requested a consultation by the Study Endpoints and Labeling Development (SEALD) review team regarding the adequacy of the patient-reported outcomes (PRO) instrument, the Impact of Weight on Quality of Life (IWQOL-Lite), to support claims of treatment benefit in obese patients.

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.[16]

14 Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol. 2003 May;56(5):395-407.
15 Crosby RD, Kolotkin RL, Williams GR. An integrated method to determine meaningful changes in health-related quality of life. J Clin Epidemiol. 2004 Nov;57(11):1153-60.
16 Piault-Louis E. Study Endpoint Review for NDA 200063 Bupropion/Naltrexone (Contrave) 09 Nov 2010

This SEALD consult concludes that the IWQOL-Lite questionnaire lacks content validity to assess" health related quality of life" (HRQoL) changes as a result of weight-loss interventions and, thus, are not "fit for purpose" to support labeling claims. Therefore, SEALD recommends removing any claim of treatment efficacy supported by this questionnaire from the label.

5.1.5.9 Control of Eating (COE) questionnaire Item 19

The Control of Eating (COE) questionnaire[17] is a 21-item self-report visual analog scale designed to assess food cravings. A food craving was defined as a strong urge to eat a particular food or drink. Subjects were instructed to read each question carefully and place a mark at the point that best represented their experience over the preceding 7 days using a 100-mm line with extremes of 0 (not at all) to 100 (extremely or very often or after every one). Item 19 asked "Generally, how difficult has it been to control your eating?" and Orexigen states that Item 19 represents a summary measure of the subject's perception of eating control.

There were significant differences for the NB32 dose in Trial NB-301 (LS Mean difference from placebo -5.8) but not for NB16 or for NB32 in other trials.

The patient-reported outcomes instrument, the Control of Eating questionnaire (COE), is intended to be used as evaluative measure to support claim of treatment benefit in obese patients. FDA requested from Orexigen adequate evidence of the development and validation of the COE in the intended population. Orexigen responded that there is no published data on the development process or psychometric properties of the COE.

In addition, the SEALD review team concluded that the information submitted as part of this NDA fails to document that the COE is a well-defined and reliable endpoint measure. This SEALD consult concludes that the COE questionnaire lacks content validity to assess "control over eating" changes as a result of weight-loss interventions and, thus, are not "fit for purpose" to support labeling claims. Therefore, SEALD recommends removing any claim of treatment efficacy supported by this questionnaire from the label.[16]

5.1.5.10 Food Craving Inventory (FCI) questionnaire

The Food Craving Inventory (FCI) questionnaire[18] is a 33-item self-report measure designed to assess specific food cravings. The original 28-item scale did not include cooked vegetables (item 5), fruit juices (item 12), raw vegetables (item 18), canned fruit (item 21), or raw fruit (item 29). FCI is organized into 4 subscales (high fats, sweets, carbohydrates/starches, and fast-food fats). Subjects rated each item on a 5 point scale.

17 Hill AJ, Blundell JE: Control of eating questionnaire: An assessment device. Unpublished Questionnaire. University of Leeds, 2006.
18 White MA, Whisenhunt BL, Williamson DA, Greenway FL, Netemeyer RG: Development and validation of the food craving inventory. Obes Res 2002; 10: 107-14.

No statistically significant treatment effects were observed between treatment groups in food craving frequency for the Sweets and Carbohydrate/Starches subscales of the FCI.

5.1.5.11 Inventory of Depressive Symptomatology Subject-Rated (IDS-SR) questionnaire

The Inventory of Depressive Symptomatology Subject-Rated (IDS-SR) questionnaire[19] is a 30-item questionnaire designed to assess changes in mood or depressive symptoms. This self-rated instrument was used in the trials as a screening instrument and an assessment of both efficacy and safety. Subjects were asked to circle the response that best described their symptons over the course of the past 7 days. Most items were scored using a 4 point scale. Baseline IDS-SR scores in all trials were in the normal range, indicating that the subjects participating in the Phase 3 trials had minimal or no depressive symptomatology. There were minimal changes from baseline in the IDS-SR total score which did not reach statistical significance.

5.1.6 Other Endpoints

NB-301 Body Composition Substudy

1. compare the change from baseline to Week 52 in body composition, measured by total fat mass (kg) using DEXA, in the pooled active treatment groups (NB16 and NB32) and the placebo group
2. compare the placebo and the pooled active treatment group in the change from baseline of whole body total percent fat and total lean mass (DEXA assessments), and visceral fat mass (CT assessment).

In this substudy, NB treated subjects experienced a change in total body weight from baseline of -6.97 kg (LS mean change) for NB and -2.01 kg for placebo, and the LS mean difference between NB and placebo was -4.96 kg (95% CI, -7.63, -2.28). The LS mean percent change from baseline was -7.18% for NB and -2.11% for placebo, and the LS mean difference between NB and placebo was -5.07% (95% CI, -7.78, -2.36).

The pooled active treatment groups (NB16 and NB32) compared with placebo showed

- a greater decrease in total fat mass (p=0.001)
- a greater decrease in whole body total percent body fat (p=0.006)
- a greater decrease in visceral adipose tissue mass (p=0.037)
- a greater decrease in whole body total lean mass (p=0.003)

The whole body total percent lean mass was increased in the NB treated group (LS mean 2.44%) compared with placebo (LS mean 0.77%) (LS mean difference from placebo = 1.66; p=0.006, 95% CI, 0.48, 2.85), suggesting that the total weight loss was primarily due to a reduction in adipose tissue.

19 Rush AJ, Gullion CM, Basco MR, Jarrett RN, Trivedi MH: The Inventory of Depressive Symptomatology (IDS): Psychometric Properties. Psychol Med. 1996 May; 26(3): 477-86.

Table 21: Body Composition, Change from Baseline to Endpoint in Trial NB-301 Substudy (Full Analysis Set)

Statistic	Placebo	NB
Primary Endpoints: Total Fat Mass (kg)	n=45	n=79
Baseline mean (SD)	41.30 (9.20)	39.39 (6.90)
Change from baseline, LS Mean (SE)	-1.44 (0.77)	-4.72 (0.61)
LS Mean difference from placebo (SE)	--	-3.28 (0.98)
95% CI	--	(-5.22, -1.35)
p-value	--	0.001
Secondary Endpoints:		
Whole Body Total Percentage Fat (%)	N=45	N=79
Baseline mean (SD)	41.80 (6.61)	41.10 (5.20)
Change from baseline, LS Mean (SE)	-0.77 (0.47)	-2.44 (0.38)
LS Mean difference from placebo (SE)	--	-1.66 (0.60)
95% CI	--	(-2.85, -0.48)
p-value	--	0.006
Visceral Adipose Tissue Mass (kg)	N=24	N=34
Baseline mean (SD)	4.04 (1.65)	3.74 (1.59)
Change from baseline, LS Mean (SE)	-0.18 (0.13)	-0.55 (0.12)
LS Mean difference from placebo (SE)	--	-0.37 (0.17)
95% CI	--	(-0.72, -0.02)
p-value	--	0.037
Whole Body Total Lean Mass (kg)	N=45	N=79
Baseline mean (SD)	57.38 (9.89)	56.96 (11.71)
Change from baseline, LS Mean (SE)	-0.60 (0.35)	-1.94 (0.28)
LS Mean difference from placebo (SE)	--	-1.34 (0.45)
95% CI	--	(-2.22, -0.46)
p-value	--	0.003

Source: Orexigen's Table ISE.301SS.1-4
Abbreviations: NB =Naltrexone SR 16 mg/Bupropion SR 360 mg and Naltrexone SR 32 mg/Bupropion SR 360 mg, SD=Standard Deviation, LS Mean=Least Squares Mean, SE=Standard Error, CI=Confidence Interval
Notes:
(1) p-value is based on Type III sums of squares from the ANCOVA model: Treatment, Pooled Study Center, and Baseline.
(2) The full analysis set includes all subjects who were randomized, had a baseline and had at least one post-baseline body Composition analysis.
(3) Results are based on LOCF method during the double-blind treatment phase.

5.1.7 Subpopulations

Orexigen pooled the data from the four Phase 3 trials to evaluate the effects on subpopulations of treatment with NB (both 16 mg in Trial NB-301 and 32 mg from all trials) compared with placebo and NB32 compared with placebo.

5.1.7.1. Gender, Race, Age and BMI class
The subject demographic subgroups included:

- Gender: Male, Female.

- Race: White, Black or African American, and Other.
- Age: 18-44, 45-64, and ≥65 years.
- BMI: <30, 30 to <35, 35 to <40, ≥40 kg/m^2.

The comparisons of NB pooled (16 and 32 mg) to placebo and NB32 to placebo were analyzed for each demographic subgroup for the co-primary variables of percent decrease from baseline in body weight and the proportion of subjects with a weight loss from baseline of ≥5%.

The comparisons of NB pooled (16 and 32 mg) to placebo in the percent decrease from baseline in body weight showed that for all the subgroups (based on gender, race, age, and BMI), NB was generally more effective than placebo. A treatment by gender interaction (p=0.096) and a treatment by race interaction (p<0.001) suggested a greater reduction in weight for females and the White race. A treatment by BMI interaction (p=0.040) suggested a greater reduction in weight for subjects with BMI <30 kg/m^2 (n=55).

The results were similar for the NB32 to placebo comparison for subgroups (see Table below), except that the treatment by subgroup interaction was not evident for females vs. males and the NB32 treatment effect compared with placebo for the "Other" race was significant (p=0.046).

Table 22: Body Weight (kg), Percent Change from Baseline to Endpoint by Subject Demographics for Combined Phase 3 Trials NB32 and Placebo (Full Analysis Set)

Statistic	**Subject Demographics**					
By Gender	**Male**			**Female**		
	Placebo (n=243)	NB32 (n=388)		Placebo (n=1076)	NB32 (n=1655)	
Baseline mean (SD)	113.93 (15.63)	116.76 (17.47)		97.30 (13.69)	97.68 (14.32)	
% change from baseline, LS Mean (SE)	-2.18 (0.39)	-6.12 (0.30)		-2.38 (0.23)	-7.17 (0.19)	
LS Mean difference from placebo (SE)	-3.94 (0.48)			-4.79 (0.28)		
95% CI	(-4.88, -3.01)			(-5.34, -4.24)		
p-value	<0.001			<0.001		
Treatment by subgroup p-value	0.143					
By Race	**White**		**Black**		**Other**	
	Placebo (n=1044)	NB32 (n=1617)	Placebo (n=220)	NB32 (n=336)	Placebo (n=55)	NB32 (n=90)
Baseline mean (SD)	100.17 (15.75)	101.28 (17.05)	102.00 (13.78)	102.31(15.19)	97.44 (16.25)	97.94 (16.20)
% change from baseline, LS Mean (SE)	-2.58 (0.22)	-7.62 (0.18)	-1.34 (0.40)	-4.59 (0.31)	-2.40 (1.04)	-5.08 (0.85)
LS Mean difference from placebo (SE)	-5.04 (0.28)		-3.52 (0.49)		-2.68 (1.33)	
95% CI	(-5.58, -4.49)		(-4.22, -2.29)		(-5.32, -0.05)	
p-value	<0.001		<0.001		0.046	

Treatment by subgroup p-value	<0.001					
By Age (years)	**18-44**		**45-64**		**≥65**	
	Placebo (n=599)	NB32 (n=878)	Placebo (n=689)	NB32 (n=1120)	Placebo (n=31)	NB32 (n=45)
Baseline mean (SD)	101.47 (15.36)	102.55 (16.18)	99.53 (15.43)	100.55 (16.99)	97.42 (17.53)	95.73 (18.72)
% change from baseline, LS Mean (SE)	-1.34 (0.33)	-6.24 (0.28)	-2.94 (0.27)	-7.37 (0.21)	-4.67 (1.50)	-7.88 (1.19)
LS Mean difference from placebo (SE)	-4.90 (0.36)		-4.43 (0.34)		-3.21 (1.41)	
95% CI	(-5.61, -4.20)		(-5.10, -3.77)		(-6.02, -0.40)	
p-value	<0.001		<0.001		0.026	
Treatment by subgroup p-value	0.621					

Source: Orexigen's Table 30 and Table ISE.SGP.1-1B
AbbreviationsNB32=Naltrexone SR 32 mg/Bupropion SR 360 mg, SD=Standard Deviation, LS Mean=Least Squares Mean, SE=Standard Error, CI=Confidence Interval
Notes:
(1) Within stratum p-values are the pairwise comparisons of the LS Means from ANCOVA model: Treatment, Study, and Baseline.
(2) Type III sums of squares from ANCOVA model: Treatment, Study, Baseline, Subgroup, Treatment-by-Subgroup for interaction and subgroup p-values.
(3) The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug.
(4) Results are based on LOCF method while on study drug.

The comparisons of NB pooled (16 and 32 mg) to placebo in the proportion of subjects with a weight loss from baseline of ≥5% showed that for all the subgroups (based on gender, race, age, and BMI), NB was more effective than placebo.

The results were similar for the NB32 to placebo comparison for subgroups. In all subgroups, the proportion of subjects experiencing ≥5% decrease in total body weight was greater than 40% (40.2% to 57.1%) for NB32 and more than double the proportion observed with placebo treatment (14.6% to 24.1%). The differences from placebo were numerically greater for all subgroups when comparing the data of the higher dose only (NB32) to both doses pooled NB (16 and 32). No treatment by subgroup interactions were observed in either the pooled NB or the NB32 analyses.

Table 23: Body Weight (kg), Proportion of Subjects with ≥ 5% Decrease from Baseline to Endpoint by Subject Demographics for Combined Phase 3 Trials NB32 and Placebo (Full Analysis Set)

Statistic	**Subject Demographics**					
By Gender	**Male**			**Female**		
	Placebo (n=243)	NB32 (n=388)		Placebo (n=1076)	NB32 (n=1655)	
No. (%) with ≥ 5% decrease	42 (17.28%)	184 (47.42%)		232 (21.56%)	901 (54.44%)	
95% CI	(12.53%, 22.04%)	(42.45%, 52.39%)		(19.10%, 24.02%)	52.04%, 56.84%)	
Odds ratio (vs. placebo)	4.32			4.37		

95% confidence limit for odds ratio	(2.93, 6.37)			(3.67, 5.20)		
p-value	<0.001			<0.001		
Treatment by subgroup p-value	0.980					
By Race	**White**		**Black**		**Other**	
	Placebo (n=1044)	NB32 (n=1617)	Placebo (n=220)	NB32 (n=336)	Placebo (n=55)	NB32 (n=90)
No. (%) with ≥ 5% decrease	231 (22.13%)	911 (56.34%)	32 (14.55%)	135 (40.18%)	11 (20.00%)	39 (43.33%)
95% CI	(19.61%, 24.64%)	(53.92%, 58.76%)	(9.89%, 19.20%)	34.94%, 45.42%)	(9.43%, 30.57%)	33.10%, 53.57%)
Odds ratio (vs. placebo)	4.60		3.95		3.06	
95% confidence limit for odds ratio	(3.86, 5.49)		(2.56, 6.10)		(1.40, 6.69)	
p-value	<0.001		<0.001		0.005	
Treatment by subgroup p-value	0.535					
By Age (years)	**18-44**		**45-64**		**≥65**	
	Placebo (n=599)	NB32 (n=878)	Placebo (n=689)	NB32 (n=1120)	Placebo (n=31)	NB32 (n=45)
No. (%) with ≥ 5% decrease	101 (16.86%)	423 (48.18%)	166 (24.09%)	639 (57.05%)	7 (22.58%)	23 (51.11%)
95% CI	(13.86%, 19.86%)	(44.87%, 51.48%)	20.90%, 27.29%)	54.15%, 59.95%)	(7.86%, 37.30%)	(36.51%, 65.72%)
Odds ratio (vs. placebo)	4.64		4.23		3.84	
95% confidence limit for odds ratio	(3.60, 5.97)		(3.43, 5.23)		(1.35, 10.96)	
Treatment by subgroup p-value	0.798					

Source: Orexigen's Table 31 and Table ISE.SGP.1-2B
Abbreviations: NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg, CI=Confidence Interval
Notes:
(1) Logistic Regression model: Treatment, Subgroup, Baseline Body Weight, Treatment-by-Subgroup for interaction and Subgroup p-values.
(2) If sample size is larger than or equal to 20, then the 95% Confidence Interval is calculated by the normal approximation to the binomial distribution; otherwise, the exact binomial confidence interval is used.
(3) Logistic Regression model: Treatment and Baseline Body Weight for within-stratum p-values
(4) The full analysis set includes all subjects who were randomized, had a baseline body weight measurement, and had at least one post-baseline body weight measurement while on study drug. Results are based on LOCF method while on study drug.

5.1.7.2 Hypertension, Dyslipidemia, Metabolic Syndrome, Impaired Fasting Glucose
The baseline disease characteristics were based on the presence or absence of hypertension, dyslipidemia, metabolic syndrome, and impaired fasting glucose (defined as glucose ≥100 mg/dL at baseline). The comparisons of NB pooled to placebo and NB32 to placebo were analyzed for each baseline disease characteristic for the co-primary variables of percent decrease from baseline in body weight and the proportion of subjects with ≥5% weight loss from baseline.

For all the subgroups based on the presence or absence of baseline diseases, NB was more effective than placebo in the percent change in weight from baseline. There was a marginal treatment by hypertension interaction (p=0.064) and a significant treatment by impaired fasting

glucose interaction (p=0.014) suggesting a greater reduction in weight for subjects without hypertension and without impaired fasting glucose.

For all the subgroups based on the presence or absence of baseline diseases, NB was more effective than placebo in the proportion of subjects with a ≥5% weight loss from baseline. There were no treatment by subgroup interactions.

5.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

NB-301 evaluated the two different doses of naltrexone (16 mg and 32 mg) in a sustained release formulation combined with bupropion SR 360 mg for up to 56 weeks. This trial met FDA's categorical endpoint for efficacy (i.e., proportion of subjects that lose ≥ 5% of baseline body weight is ≥ 35%, is ~2x the placebo group, and the difference is statistically significant) but did not meet FDA's continuous endpoint for efficacy (i.e., statistically significant difference in mean weight loss between NB and placebo is ≥ 5%).

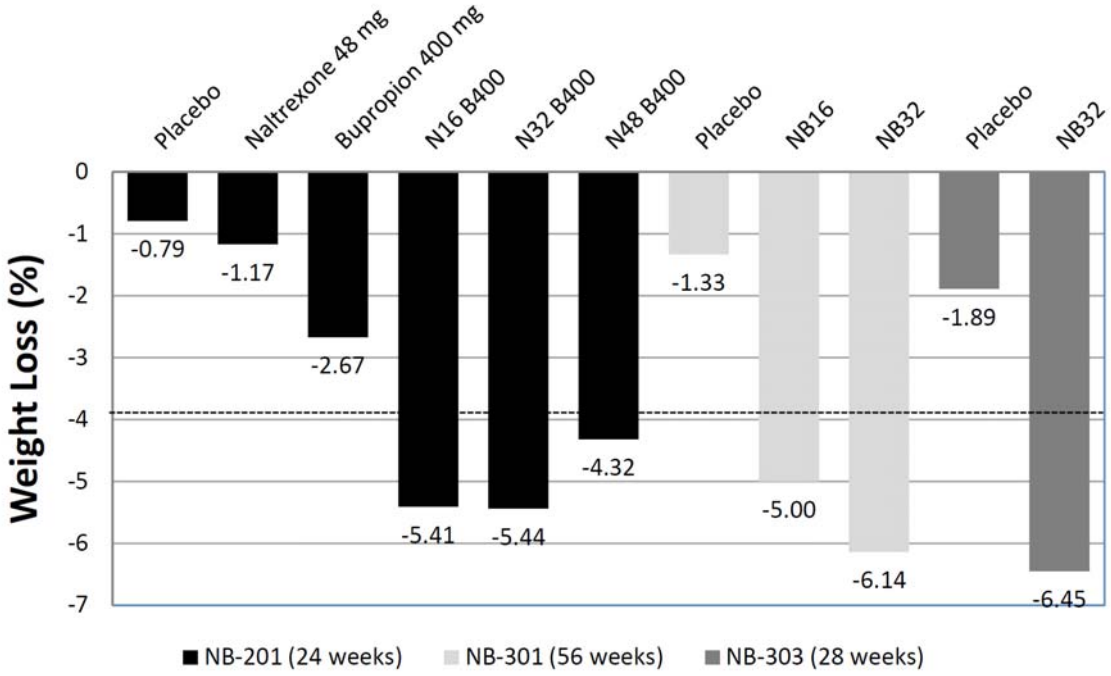
The NB32 combination showed greater treatment effects on the co-primary endpoints than the NB16 treatment in Trial NB-301.

- The NB32 dose demonstrated greater efficacy in mean weight loss (LS mean difference from placebo of -4.81%) compared with NB16 (-3.67%) (p=0.008).
- A greater proportion of subjects achieved 5% or greater weight loss in NB32 (48.0%) compared with NB16 (39.5%) (p=0.010).

The efficacy results seen in the Phase 3 trials were not entirely consistent for the NB16 dose with those in the Phase 2 Trial NB-201. The placebo-subtracted LS mean percent change from baseline at 24 weeks in Trial NB-201 was -4.62 (95% CI: -6.24, -2.99) for N16/B400. These results were better than the results observed at 56 weeks in Trial NB-301 where the placebo-subtracted LS mean percent change from baseline for NB16 was -3.67 (95% CI: -4.50, -2.85). The efficacy results seen in the Phase 3 trials were consistent for the NB32 dose with those in the Phase 2 Trial NB-201. The placebo-subtracted LS mean percent change from baseline at 24 weeks in Trial NB-201 was -4.65 (95% CI: -6.20, -3.09) for N32/B400. These results were comparable to the results observed at 56 weeks in Trial NB-301 where the placebo-subtracted LS mean percent change from baseline for NB32 was -4.81 (95% CI: -5.63, -3.99) and in trial NB-303 at 28 weeks where the placebo subtracted LS mean percent change from baseline for NB32 was -4.56 (95% CI: -5.19, -3.93).

The figure below shows the percent change from baseline in body weight for Trials NB-201, NB-301, and NB-303 to illustrate the more than additive effects of naltrexone and bupropion on weight loss, as well as the dose-response between NB16 and NB32 doses and the consistency of response to the NB32 dose across the trials. Of note, there was no dose response between naltrexone 16 mg and 32 mg noted in the 24-week duration Trial NB-201. However, a dose relationship between those doses was seen in the 56-week Trial NB-301.

Figure 3: Body Weight (kg), Percent Change from Baseline to Endpoint (Trials NB-201, NB-301, and NB-303)

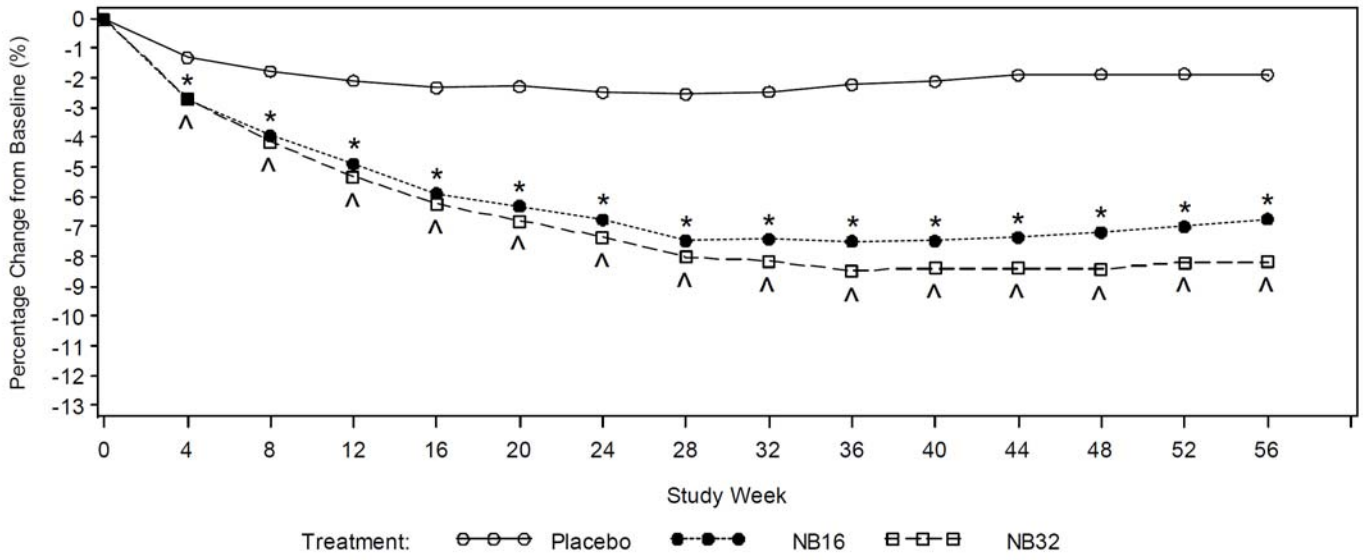


Source: Orexigen's Figure 2.7.3-3
Endpoint was Week 24 for Trial NB-201 and Week 56 for NB-301 and Week 28 for NB-303. NB-201 results are for the intent-to-treat analysis set; NB-301 and NB-303 results are for the full analysis set.

5.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy was evaluated by Orexigen through examination of the time course of weight loss across the four Phase 3 trials and for both doses in Trial NB-301. Greater weight loss, as early as Week 4, was observed for subjects receiving NB treatment. Maximum weight loss was observed after 28 to 40 weeks of treatment (except in Trial NB-304 where it was achieved earlier). In Trial NB-301 treatment with NB16 and NB32 resulted in comparable weight loss through Week 28, although beyond that point weight loss with NB16 appeared to be less than NB32 (see Figure below).

Figure 4: Body Weight (kg), Percent Change from Baseline by Visit (Completer's Analysis Set) Trial NB-301



Source: Orexigen's Figure nb-301:14.2-6
Abbreviation: NB16=naltrexone SR 16 mg/bupropion SR 360 mg and NB32=naltrexone SR 32 mg/bupropion 360 mg.
The completers analysis set include all randomized subjects who have a baseline body weight measurement and a post-baseline body weight measurement and have completed 56 weeks of treatment. Results are based on observed values for subjects completing their assessments at each visit while on study drug.
ANCOVA model: Treatment, Pooled Study Center, and Baseline.
*: p-value <0.05 (NB16 vs. Placebo), ^: p-value <0.05 (NB32 vs. Placebo).

5.1.10 Additional Efficacy Issues/Analyses

Sensitivity analyses were conducted by Orexigen on the co-primary efficacy measures to address missing data and the potential bias associated with early withdrawal from a trial. These included repeating the primary comparisons using a modified ITT analysis set (ITT analysis), a completers analysis set, a repeated measures mixed effect model, weight regain imputation, and baseline observation carried forward (BOCF) analysis.

ITT analysis: This analysis included all randomized subjects with a baseline and post-baseline body weight measurement where baseline was defined in the same manner as the primary full analysis set and endpoint was defined as the last non-missing postbaseline measurement during the double-blind treatment phase (irrespective of being on study drug at the time of the last measurement). In contrast, in the primary full analysis set endpoint was defined as the last non-missing post-baseline measurement while on study drug (LOCF).

Completers analysis: For trials NB-301, NB-303, and NB-304, this analysis set included all randomized subjects with a baseline measurement, a postbaseline body weight measurement, and who completed 56 weeks of treatment. For Trial NB-302, the completer analysis set included all

randomized subjects who had a baseline measurement and a post-baseline measurement at Week 56 while on study drug (i.e. active treatment).

Repeated measures mixed effect model: An analysis of percent (and absolute) change from baseline on total body weight loss was performed based on the LS means estimated from a repeated measures linear mixed-effects model based upon Type III sums of squares using the full analysis set and the ITT analysis set.

Weight regain imputation method: An imputation method was used to account for missing values due to drop outs. This analysis imputed an estimated 0.3 kg per month of weight regain in subjects who withdrew from the study early until the baseline weight was reached. For subjects who did not return after enrollment, the baseline was imputed for all missing values (i.e., the percent change from baseline was equal to zero for these subjects). The ANCOVA model was used to analyze the percent change from baseline and the logistic regression model was used to analyze the proportion of subjects who achieved ≥5% weight loss from baseline. This was conducted on all randomized subjects.

BOCF: An additional sensitivity analysis using all randomized subjects was conducted in which endpoint was defined as the Week 56 measurement, irrespective of being on study drug or not (Week 28 for the primary analysis of Trial NB-303). For randomized subjects who discontinued active study drug prior to Week 56 (or Week 28 for the primary analysis of Trial NB-303), endpoint was the baseline measurement (i.e., the percent change from baseline was equal to zero for these subjects).

Trial NB-301
As shown in the table below, the results of the sensitivity analyses on the completers and the ITT datasets as well as the repeated measures mixed effect model analysis, BOCF and weight regain imputation method showed statistically significant results for the active treatment groups compared with placebo ($p<0.001$).

Table 24: Body Weight (kg), Percent Change from Baseline to Endpoint Primary Analysis and Secondary Sensitivity Analysis Double-Blind Treatment Phase NB-301

	Treatment group	N	% change from Baseline LS Mean	LS Mean Difference from Placebo	p-value
Full Analysis Set	Placebo	511	-1.3		
	NB16	471	-5.0	-3.7	<0.001
	NB32	471	-6.1	-4.8	<0.001
Completers Analysis Set	Placebo	290	-1.8		
	NB16	284	-6.7	-4.9	<0.001
	NB32	296	-8.1	-6.2	<0.001
ITT Analysis Set	Placebo	536	-1.3		
	NB16	524	-4.5	-3.2	<0.001
	NB32	538	-5.4	-4.1	<0.001
Weight Regain	Placebo	581	-1.2		

	Treatment group	N	% change from Baseline LS Mean	LS Mean Difference from Placebo	p-value
Imputation Method					
	NB16	578	-3.7	-2.5	<0.001
	NB32	583	-4.6	-3.4	<0.001
Baseline-Carried-Forward Analysis	Placebo	581	-0.9		
	NB16	578	-3.3	-2.4	<0.001
	NB32	583	-4.0	-3.1	<0.001
Source: Orexigen Table ISE.301.1-6					

As shown in the table below, the results of the sensitivity analyses showed statistically significant results for the active treatment groups compared with placebo ($p<0.001$) for the proportion of subjects with ≥ 5% weight loss.

Table 25: Body Weight (kg), Proportion of Subjects with ≥5% Decrease from Baseline to Endpoint Primary Analysis and Secondary Sensitivity Analysis Double-Blind Treatment Phase NB-301

	Treatment group	N	≥5% Decrease n (%)	Odds Ratio (vs. placebo)	p-value
Full Analysis Set	Placebo	511	84 (16.4)		
	NB16	471	186 (39.5)	3.4	<0.001
	NB32	471	226 (48.0)	4.9	<0.001
Completers Analysis Set	Placebo	290	67 (23.1)		
	NB16	284	155 (54.6)	4.2	<0.001
	NB32	296	183 (61.8)	5.8	<0.001
ITT Analysis Set	Placebo	536	93 (17.4)		
	NB16	524	190 (36.3)	2.8	<0.001
	NB32	538	226 (42.0)	3.6	<0.001
Weight Regain Imputation Method	Placebo	581	78 (13.4)		
	NB16	578	175 (30.3)	2.9	<0.001
	NB32	583	203 (34.8)	3.6	<0.001
Baseline-Carried-Forward Analysis	Placebo	581	67 (11.5)		
	NB16	578	156 (27.0)	2.9	<0.001
	NB32	583	180 (30.9)	3.6	<0.001
Source: Orexigen Table ISE.301.1-7					

For Trials NB-302, NB-303, and NB-304 the results of the 5 sensitivity analyses also showed statistically significant greater weight loss and a greater proportion of subjects with ≥ 5% weight loss for the active treatment group NB32 compared with placebo.

6 Review of Safety

Safety Summary

Deaths: One subject in the NB32 group suffered a fatal myocardial infarction.

Serious[20] Adverse Events [NB (N=3239)>Pbo (N=1515)]:

- cholecystitis (NB: 6 subjects; Placebo: 1 subject)
- cellulitis (NB: 3 subjects; Placebo: 2 subjects)
- non-cardiac chest pain (NB: 3 subjects; Placebo: 1 subject)
- myocardial infarction (NB: 3 subjects; Placebo: 0 subject)
- staphylococcal infection (NB: 2 subjects; Placebo: 1 subject)
- small intestinal obstruction (NB: 2 subjects; Placebo: 1 subject)
- chest pain (NB: 2 subjects; Placebo: 1 subject)
- calculus ureteric (NB: 2 subjects; Placebo: 1 subject)
- syncope (NB: 2 subjects; Placebo: 0 subject)
- seizure (NB: 2 subjects; Placebo: 0 subject)

AEs that lead to discontinuation [NB (N=3239)>Pbo (N=1515)]:

- nausea, headache, dizziness, vomiting, insomnia, urticaria/rash, blood pressure increase/hypertension, fatigue, palpitations, abdominal pain, tremor, constipation, diarrhea, feeling jittery, and disturbance in attention

Common AEs (≥5% incidence) ≥ 2x placebo:

- nausea, constipation, vomiting, dizziness, and dry mouth

Less frequent AEs (≥2% incidence) ≥ 2x placebo:

- tremor, hot flush, tinnitus, abdominal pain upper, dysgeusia, hyperhidrosis, and palpitations

Severe[21] AEs (≥0.4% incidence) ≥ 2x placebo:

- nausea, headache, vomiting, constipation, dizziness, abdominal pain upper, migraine, and insomnia

Special Safety Topics:

Blood Pressure and Pulse

20 A serious adverse event (SAE) was defined as any event that was fatal or immediately life-threatening, resulted in or prolonged an existing hospitalization, resulted in a persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or required medical or surgical intervention to prevent one of the outcome listed above.

21 The severity of each AE was classified as mild (discomfort noted, but no disruption of normal daily activity), moderate (discomfort of sufficient severity to reduce or adversely affect normal activity), or severe (incapacitating, with inability to work or perform normal daily activity.

- 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.
- Blood pressure-related TEAEs (including hypertension and increased blood pressure terms) in both the NB32 and placebo groups were reported mostly by subjects with a history of hypertension or antihypertensive medication use at baseline, occasionally led to treatment discontinuation, and required medication in approximately two-thirds of subjects.
- 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).

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.

Seizure and Convulsions

Two subjects (2/3239, 0.06%) in the NB32 group, compared to none in the placebo group, experienced a seizure. Both subjects had no prior seizure history; one subject may have experienced a hypoglycemic seizure.

Suicide-related Events

A retrospective assessment tool of suicidality, the Columbia Classification Algorithm of Suicide Assessment (C-CASA) was used to assess AEs that could represent suicidal events (behavior and ideation) during Phase 2b and 3 trials. There were no completed suicides, suicide attempts, or preparatory acts toward imminent suicidal behavior in any treatment group. There were four events of suicidal ideation or behavior during this trial, one event (1/3239, <0.1%) in the Total NB treatment group compared to three events (3/1515, 0.2%) in the placebo treatment group.

Psychiatric Events (Depression, Anxiety, Sleep Disorders, Psychosis)

- There were a higher percentage of subjects with Psychiatric events in the Total NB group compared with the placebo group (20.8% and 15.5%, respectively).
- Psychiatric events were seen more often in subjects with a prior history of depression or anxiety in both Total NB and placebo groups than in subjects without a prior history.
- The AE incidence in the Depression subtopic was similar between treatment groups (6.0% Total NB and 5.9% placebo).
- The AE incidence in the Anxiety subtopic was greater in the Total NB group compared to placebo [186, (5.7%) and 66, (4.4%), respectively].
- The AE incidence in the Sleep Disorders subtopic was higher in the Total NB group compared with placebo (12.8% Total NB and 8.4% placebo). Insomnia was the most

frequently occurring TEAE (8.6% Total NB and 5.9% placebo) in the Sleep Disorders category.

- The AE incidence in the Psychosis disorders subtopic was higher in the Total NB group compared with placebo (0.8% Total NB and <0.1% placebo). The placebo group had only one report of potential psychosis (depersonalization) and no reports of psychosis events. Of the Total NB subjects with events in the Psychosis subtopic, 18/26 reported either dissociation (10) or agitation (8).

Neurologic/Cognitive

- There was a greater incidence of Cognitive subtopic events in the Total NB group compared to the placebo group (5.1% vs. 2.0%). None of the events were SAEs and 1.1% of Total NB group versus 0.4% of placebo subjects discontinued for a Cognitive event.
- The most common Cognitive events category was Attention Disorders (2.3% Total NB vs 0.6% placebo).
- Events in the Dizziness/Syncope subtopic were common in Total NB (10.2%) and 2.8 times more frequent than in placebo (3.6%). The single preferred term dizziness accounted for almost all reported events (10% Total NB and 3.4% placebo). Dizziness was the primary reason for discontinuation, occurring in 1.3% of Total NB and 0.3% of placebo subjects.
- Two subjects in the Total NB group reported an SAE of syncope compared to zero in placebo and three NB subjects discontinued due to syncope compared to zero in placebo.

Renal Function

- Larger mean changes in creatinine from baseline to endpoint were observed in the Total NB group compared with the placebo group (0.07 mg/dL NB vs 0.01 mg/dL placebo) and from baseline to maximum (0.15 mg/dL NB vs 0.07 mg/dL placebo). The highest mean serum creatinine levels were seen at Week 4.
- Shifts to high creatinine at any postbaseline assessment occurred in a higher percentage of subjects in the Total NB group (7.6%) compared with the placebo group (1.9%).
- There were a slightly greater percentage of subjects with Renal Disorders in the Total NB group compared with the placebo group (4.8% and 3.8%, respectively). Renal Disorders SAEs and discontinuations were infrequent.

Hepatobiliary

- The incidence of Liver and Gallbladder events was similar in the Total NB and placebo groups (1.9% and 1.7%, respectively) in the Primary Dataset and the incidence of SAEs (0.3% Total NB vs. <0.1% placebo subjects) and discontinuations (0.3% Total NB vs. 0.2% placebo subjects) were low.
- No subjects met criteria for Hy's law classification and transaminase level increases were similar between treatment groups.
- Gallbladder-related SAEs occurred in 0.3% of subjects in the Total NB group and <0.1% in the placebo group. All subjects with gallbladder-related SAE subjects were hospitalized and underwent gallbladder surgery.

Hypersensitivity Reaction/Skin Rash

The incidence of Hypersensitivity Reaction/Skin Rash events was similar in the Total NB group compared with the placebo group (13.4% and 15.2%, respectively) and there was no difference in the incidence of SAEs (≤0.1% in both groups).

6.1 Methods

6.1.1 Clinical Trials Used to Evaluate Safety

The clinical trials used to evaluate safety are the following:

1. the four Phase 3 trials (Trials NB-301, NB-302, NB-303, and NB-304), which provided for up to 56 weeks of treatment
2. the one Phase 2 trial (Trial NB-201), where the placebo-controlled period provided for up to 24 weeks of treatment.

A description of the trials is in Section 5.1.1 Methods.

6.1.2 Categorization of Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as events that occurred or worsened on or after the date of first dose until 7 days after the last confirmed dose. In the ISS, adverse events were coded using MedDRA 12.0.

Treatment-emergent AEs are discussed by dataset (Primary, Overall, Diabetic vs. Nondiabetic) and treatment phase as follows:

- Double-blind treatment phase (includes both titration and maintenance phases),
- Titration phase (TEAEs occurring within 35 days of first dose for Trial NB-303 and within 28 days for the other trials), and
- Maintenance phase (TEAEs occurring greater than 35 days of first dose for trial NB-303 and greater than 28 days for the other trials).

Treatment-emergent AEs are also discussed by severity (mild, moderate, severe).

In the NDA submission, Orexigen used the following medical concepts of interest in the Integrated Summary of Safety (ISS) within the framework of defined 'Special Topics'.

1. Blood Pressure and Pulse
2. Cardiovascular Events
3. Suicide-related Events
4. Psychiatric Events
5. Cognitive Disorders
6. Renal Function
7. Seizure and Convulsions
8. Liver and Gallbladder
9. Hypersensitivity Reaction/Skin Rash

The adverse events included within these Special Topics were defined after physician review of all adverse events reported in the Contrave Phase 2 and Phase 3 clinical studies. Based on this review, preferred terms were selected for inclusion into each Special Topic category. Standardized MedDRA Queries (SMQs) were also used when available to assist in defining terms to be included in the Special Topics.

In Orexigen's Advisory Committee briefing document, whenever possible, Orexigen regrouped the adverse event terms included under Special Topics as used in the ISS in the construct of 'Targeted Medical Events' (TMEs) based on SMQs in the review of QNEXA and SMQs in the review of LORQESS. Therefore, some of the adverse event incidences differ between this document and Orexigen's briefing document depending on which grouping of adverse events Orexigen used. The percentages will be different, but this does not change the overall conclusions for safety.

6.1.3 Pooling of Data Across Clinical Trials to Estimate and Compare Incidence

Orexigen's Integrated Summary of Safety (ISS) includes three Phase 2 and 3 integrated datasets: the primary placebo-controlled integrated safety analysis dataset, the overall NB exposure integrated safety analysis dataset, and the secondary placebo-controlled integrated safety analysis dataset (hereafter referred to as the Primary, Overall, and Nondiabetic datasets). These datasets include data from all randomized subjects who were administered at least one tablet 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 discontinued the trial. Data are presented at each of the three dose levels of naltrexone: 16 mg (N=633, two separate trials), 32 mg (N=2545, five trials) and 48 mg (N=61, one trial), as well as all NB-treated subjects (N=3239).

The **Primary** Dataset for safety includes safety data from five completed Phase 2 and 3 multicenter, randomized, double-blind, placebo-controlled, clinical trials: Trials NB-201 (excludes data during the non-double-blind extension phase), NB-301 (excludes data during the 2-week discontinuation phase), NB-302, NB-303, and NB-304. In Trial NB-303, data from subjects randomized to NB32 who failed to achieve or maintain a 5% reduction in body weight and were re-randomized to NB48 beginning at Week 28 are included in the NB32 dose, unless otherwise specified.

The **Overall** Dataset includes safety data from eight completed Phase 2 and 3 clinical trials: Trials OT-101 (includes data from the primary treatment phase and the extension phase), NB-201 (includes data from the primary treatment phase and the extension phase), NB-301, NB-302, NB-303, NB-304, and open-label studies NB-401 and NB-402. These studies were not all placebo-controlled and subjects receiving placebo or naltrexone monotherapy in OT-101 and NB-201 could be reassigned after the primary treatment period to open-label NB treatment, therefore, placebo is not included within this dataset. Relative to the Primary Dataset, the Overall Dataset includes an additional 149 subjects exposed to NB32 (from NB-401, NB-402, and NB-201 after reassignment) and 85 subjects exposed to NB50 (from OT-101).

The **Nondiabetic** dataset is the Primary dataset minus Trial NB-304 (which enrolled subjects with diabetes) and this dataset will be compared to Trial NB-304, conducted in patients with type 2 diabetes mellitus to identify any important differences in the safety profile of NB between subjects with and without diabetes.

6.2 Adequacy of Safety Assessments

6.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the Primary Dataset, there were 3239 subjects exposed to NB in dose groups of NB16 (633 subjects), NB32 (2545 subjects), or NB48 (61 subjects), and 1515 subjects exposed to placebo.

The mean exposure, in weeks, was similar across dose and treatment groups (37.6 placebo, 33.0 NB16, 36.4 NB32, and 35.4 weeks Total NB) for placebo, NB32 and Total NB. The median exposure, in weeks, was similar across dose and treatment groups for placebo (55 weeks), NB32 (56 weeks) and Total NB (55 weeks). Median exposure for the NB16 group was 32 weeks.

FDA's 2007 draft guidance entitled Developing Products for Weight Management states that a reasonable estimation of safety generally can be made when a total of ~ 3000 subjects are randomized to active doses of the product and no fewer that 1500 subjects are randomized to placebo for 1 year of treatment. The extent of exposure for the NB development program satisfies the draft guidance.

6.2.2 Routine Clinical Testing

Safety evaluations in these trials, including vital signs, clinical laboratory tests, ECGs and physical examinations, are detailed in Appendix B.

6.3 Major Safety Results

6.3.1 Deaths

One death was reported in the NB clinical development program. Subject 099-NB-301-003, a 65-year-old White male in the NB32 group, with a past medical history of active gout, hypercholesterolemia, hypertension, idiopathic bradycardia, arthralgia, and psoriasis, experienced a fatal myocardial infarction on Day 324. Relevant concurrent medications included lisinopril, lovastatin, acetylsalicylic acid, ibuprofen, and naproxen sodium. The baseline BMI

was 37 kg/m^2 and the waist circumference was 123 cm. The subject never used nicotine/tobacco products and reported an average weekly consumption of 1 bottle per week of beer. Lipid laboratories were obtained at screening, Day 1, Day 22 ((b) (6)), and Day 190 ((b) (6)). With the exception of a low HDL cholesterol value at screening only (39 mg/dL [reference range: 40 – 80 mg/dL]), the lipid values were within the normal ranges. High sensitivity CRP was obtained at Day 1 and on Day 190; both values were within the normal range.

At baseline, the subject's screening ECG was abnormal but not felt to be clinically significant, with sinus bradycardia, sinus arrhythmia, and borderline primary AV block (PR interval = 200 msec). Intermittently during the trial, the subject's blood pressure increased from the baseline value of 139/83, with values of 148/82 at Week 8, 142/76 at Week 20, and 156/82 at Week 28, returning to normal in between. Starting at Week 36, his blood pressure was consistently increased, with values of 165/80 (Week 36), 152/78 (Week 40) and 150/78 (Week 44). The subject remained bradycardic throughout the trial, with pulse ranging from 41 – 57 bpm. A table of the subject's blood pressure and pulse rates by visit for the entire trial is provided below.

Table 26: Blood Pressure and Pulse Rates by Visit for Subject 099-NB-301-003

Visit	Blood Pressure (mm Hg)	Pulse (beats per minute)
Screening	137/79	43
Baseline	139/83	43
Week 4	135/78	50
Week 8	148/82*	57
Week 12	133/79	55
Week 16	133/77	47
Week 20	142/76*	43
Week 24	134/77	49
Week 28	156/82*	47
Week 32	136/75	49
Week 36	165/80*	41
Week 40	152/78*	41
Week 44	150/78*	43

*highlighted blood pressures are hypertensive readings per JNC7

Shortly after a study visit on Day 312 (Week 44), the subject's wife informed the study site that the subject had experienced chest pain, and that he had made an appointment to see his primary care physician. On Day 324, the subject experienced a fatal myocardial infarction during a camping trip at a remote location.

Patient 099-NB-301-003 had a baseline (Day 1) body weight of 124 kg and a body weight of 100 kg at last visit (Week 44). Therefore, the subject lost 24 kg (approximately 53 pounds) from baseline to last visit. The last dose of study drug was on Day 324. Other AEs experienced by this subject included insomnia (Days 1-5), decreased appetite (Days 2-ongoing), dizziness (Days 22-135), nausea (Days 22-135), and joint sprain (Days 25-135). No additional cardiovascular-related TEAEs were recorded.

Reviewer comment: This subject had underlying risk factors for cardiac disease, however it is concerning that his systolic blood pressure increased despite significant weight loss.

6.3.2 Nonfatal Serious Adverse Events

The incidence of SAEs was higher in the Total NB group compared with the placebo group in all phases (double-blind treatment, titration, and maintenance phase). In the double-blind treatment phase of the 4754-subject Primary Dataset, 99 subjects (74/3239 [2.3%] NB and 25/1515 [1.7%] placebo) experienced treatment-emergent SAEs during the defined reporting period (between first dose and 7 days after the last dose)[22] and 13 subjects (11 NB and 2 placebo) experienced SAEs after the defined reporting period. The total tally for SAEs regardless of a pre-defined reporting period is NB: 85/3239 [2.6%] vs Placebo: 27/1515 [1.8%]. Treatment-emergent SAEs were reported in a higher percentage of subjects in the NB32 group than in the NB16 group (2.5% vs. 1.6%, respectively). No SAEs were reported in the NB48 group (N=61).

SAEs occurring in more than two subjects in both the Total NB and placebo groups combined were cholecystitis (6 and 1 subjects, respectively), cellulitis (3 and 2, respectively), non-cardiac chest pain (3 and 1, respectively), myocardial infarction (3 and 0, respectively), staphylococcal infection (2 and 1, respectively), small intestinal obstruction (2 and 1, respectively), chest pain (2 and 1, respectively), and calculus ureteric (2 and 1, respectively). In addition, syncope was reported in 2 (<0.1%) NB32 subjects and seizure was reported in 2 (<0.1%) NB32 subjects (one convulsion and one grand mal convulsion) with no reports of syncope or seizure in subjects on placebo. Cholecystitis was the only SAE reported for more than three subjects in the Total NB group, and occurred at a 0.2% incidence in the NB32 group (0% NB16 group and <0.1% placebo). Cellulitis, myocardial infarction, and non-cardiac chest pain occurred in three subjects (<0.1%) in the Total NB group. All other SAEs were reported at an incidence ≤0.1% in the Total NB group.

Table 27: Incidence of Treatment-Emergent Serious Adverse Events Across Treatment Groups by Phase: Primary Dataset

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Double-Blind Treatment Phase				
Subjects with any SAE	**25 (1.7%)**	**10 (1.6%)**	**64 (2.5%)**	**74 (2.3%)**
Infections and Infestations	**4 (0.3%)**	**3 (0.5%)**	**13 (0.5%)**	**16 (0.5%)**
Cellulitis	2 (0.1%)	0	3 (0.1%)	3 (0.1%)
Diverticulitis	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Gastroenteritis viral	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Staphylococcal infection	1 (<0.1%)	0	2 (<0.1%)	2 (<0.1%)
Bacterial infection	0	0	1 (<0.1%)	1 (<0.1%)
Bronchitis	0	0	1 (<0.1%)	1 (<0.1%)

22 In Orexigen's Advisory Committee briefing document they report the incidence of SAEs as 2.2% for Total NB and 2.7% for placebo. These calculations are based on the number of patients with adverse events as the denominator for each treatment group. The percentages in the FDA briefing document used the total number of patients in the primary safety analysis set in each treatment as the denominator.

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Bursitis infective	0	0	1 (<0.1%)	1 (<0.1%)
Enterocolitis infectious	0	0	1 (<0.1%)	1 (<0.1%)
Gastroenteritis	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Infection	0	1 (0.2%)	0	1 (<0.1%)
Lobar pneumonia	0	0	1 (<0.1%)	1 (<0.1%)
Meningitis viral	0	0	1 (<0.1%)	1 (<0.1%)
Respiratory tract infection viral	0	0	1 (<0.1%)	1 (<0.1%)
Urinary tract infection	0	0	1 (<0.1%)	1 (<0.1%)
Hepatobiliary Disorders	**1 (<0.1%)**	**1 (0.2%)**	**9 (0.4%)**	**10 (0.3%)**
Cholecystitis	1 (<0.1%)	0	6 (0.2%)	6 (0.2%)
Cholecystitis chronic	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Biliary colic	0	0	1 (<0.1%)	1 (<0.1%)
Cholelithiasis	0	0	1 (<0.1%)	1 (<0.1%)
Hepatitis cholestatic	0	0	1 (<0.1%)	1 (<0.1%)
Gastrointestinal Disorders	**1 (<0.1%)**	**2 (0.3%)**	**5 (0.2%)**	**7 (0.2%)**
Gastrointestinal haemorrhage	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Small intestinal obstruction	1 (<0.1%)	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Abdominal pain	0	0	1 (<0.1%)	1 (<0.1%)
Duodenal ulcer	0	0	1 (<0.1%)	1 (<0.1%)
Epiploic appendagitis	0	0	1 (<0.1%)	1 (<0.1%)
Inguinal hernia, obstructive	0	0	1 (<0.1%)	1 (<0.1%)
Injury, Poisoning, and Procedural Complications	**3 (0.2%)**	**2 (0.3%)**	**5 (0.2%)**	**7 (0.2%)**
Ankle fracture	1 (<0.1%)	1 (0.2%)	0	1 (<0.1%)
Compression fracture	0	0	1 (<0.1%)	1 (<0.1%)
Foot fracture	0	1 (0.2%)	0	1 (<0.1%)
Joint dislocation	0	1 (0.2%)	0	1 (<0.1%)
Joint injury	0	0	1 (<0.1%)	1 (<0.1%)
Snake bite	0	0	1 (<0.1%)	1 (<0.1%)
Tendon rupture	0	0	1 (<0.1%)	1 (<0.1%)
Whiplash injury	0	0	1 (<0.1%)	1 (<0.1%)
Rib fracture	1 (<0.1%)	0	0	0
Spinal fracture	1 (<0.1%)	0	0	0
Tibia fracture	1 (<0.1%)	0	0	0
Nervous System Disorders	**3 (0.2%)**	**0**	**7 (0.3%)**	**7 (0.2%)**
Syncope	0	0	2 (<0.1%)	2 (<0.1%)
Convulsions	0	0	1 (<0.1%)	1 (<0.1%)
Grand mal convulsion	0	0	1 (<0.1%)	1 (<0.1%)
Migraine	0	0	1 (<0.1%)	1 (<0.1%)
Paraesthesia	0	0	1 (<0.1%)	1 (<0.1%)
Radiculopathy	0	0	1 (<0.1%)	1 (<0.1%)
Cerebrovascular accident	1 (<0.1%)	0	0	0
Cervical myelopathy	1 (<0.1%)	0	0	0
Dizziness	1 (<0.1%)	0	0	0
Cardiac Disorders	**4 (0.3%)**	**0**	**6 (0.2%)**	**6 (0.2%)**
Myocardial infarction	0	0	3 (0.1%)	3 (0.1%)
Cardiac failure	0	0	1 (<0.1%)	1 (<0.1%)
Coronary artery occlusion	0	0	1 (<0.1%)	1 (<0.1%)
Palpitations	0	0	1 (<0.1%)	1 (<0.1%)

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Angina pectoris	2 (0.1%)	0	0	0
Arrhythmia	1 (<0.1%)	0	0	0
Atrial fibrillation	2 (0.1%)	0	0	0
Pericardial effusion	1 (<0.1%)	0	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**6 (0.2%)**	**6 (0.2%)**
Asthma	0	0	1 (<0.1%)	1 (<0.1%)
Bronchospasm	0	0	1 (<0.1%)	1 (<0.1%)
Chronic obstructive pulmonary disease	0	0	1 (<0.1%)	1 (<0.1%)
Dyspnoea exertional	0	0	1 (<0.1%)	1 (<0.1%)
Dyspnoea	0	0	1 (<0.1%)	1 (<0.1%)
Pulmonary embolism	0	0	1 (<0.1%)	1 (<0.1%)
General Disorders and Administrative Site Conditions	**3 (0.2%)**	**2 (0.3%)**	**3 (0.1%)**	**5 (0.2%)**
Non-cardiac chest pain	1 (<0.1%)	1 (0.2%)	2 (<0.1%)	3 (<0.1%)
Chest pain	1 (<0.1%)	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Chest discomfort	1 (<0.1%)	0	0	0
Neoplasms Benign, Malignant, and Unspecified	**3 (0.2%)**	**1 (0.2%)**	**4 (0.2%)**	**5 (0.2%)**
Breast cancer in situ	0	1 (0.2%)	0	1 (<0.1%)
Breast cancer	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Colon cancer	0	0	1 (<0.1%)	1 (<0.1%)
Meningioma	0	0	1 (<0.1%)	1 (<0.1%)
Multiple myeloma	0	0	1 (<0.1%)	1 (<0.1%)
Oesophageal carcinoma	1 (<0.1%)	0	0	0
Uterine leiomyoma	1 (<0.1%)	0	0	0
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**3 (0.1%)**	**3 (<0.1%)**
Intervertebral disc protrusion	0	0	2 (<0.1%)	2 (<0.1%)
Back pain	0	0	1 (<0.1%)	1 (<0.1%)
Rotator cuff syndrome	0	0	1 (<0.1%)	1 (<0.1%)
Renal and Urinary Disorders	**1 (<0.1%)**	**0**	**3 (0.1%)**	**3 (<0.1%)**
Calculus ureteric	1 (<0.1%)	0	2 (<0.1%)	2 (<0.1%)
Nephrolithiasis	0	0	1 (<0.1%)	1 (<0.1%)
Reproductive System and Breast Disorders	**2 (0.1%)**	**0**	**3 (0.1%)**	**3 (<0.1%)**
Menorrhagia	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Ovarian cyst	0	0	1 (<0.1%)	1 (<0.1%)
Uterine prolapse	0	0	1 (<0.1%)	1 (<0.1%)
Ovarian Mass	1 (<0.1%)	0	0	0
Metabolism and Nutrition Disorders	**0**	**0**	**2 (<0.1%)**	**2 (<0.1%)**
Dehydration	0	0	2 (<0.1%)	2 (<0.1%)
Ear and labyrinth disorders	**0**	**0**	**1 (<0.1%)**	**1 (<0.1%)**
Vertigo	0	0	1 (<0.1%)	1 (<0.1%)
Psychiatric disorders	**0**	**0**	**1 (<0.1%)**	**1 (<0.1%)**
Anxiety	0	0	1 (<0.1%)	1 (<0.1%)
Immune system disorders	**1 (<0.1%)**	**0**	**0**	**0**
Anaphylactic reaction	1 (<0.1%)	0	0	0

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Investigations	**1 (<0.1%)**	**0**	**0**	**0**
Troponin increased	1 (<0.1%)	0	0	0
Surgical and medical procedures	**1 (<0.1%)**	**0**	**0**	**0**
Knee arthroplasty	1 (<0.1%)	0	0	0

Data Source: Applicant's Tables ISS.P.6.2-3.2, ISS.P.6.2-1.1, and ISS.P.6.2-2.2.
Treatment-emergent SAEs were defined as SAEs that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]).
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48; SAE=serious adverse event.

Post-treatment Serious Adverse Events

A total of 13 subjects had a post-treatment SAE (occurred >7 days after last treatment): 11 in the NB group and 2 in the placebo group). No single SAE was reported in more than one subject. It is common in safety applications for SAEs to be collected for 30 days after the last dose of study drug. The highlighted SAEs in the table below are all within the 30-day window. This would add 7 SAEs to the Total NB group and 1 SAE to the Placebo group—bringing the total SAEs to NB: 81/3239 [2.5%] vs Placebo: 26/1515 [1.7%].

Table 28: Post-treatment Serious Adverse Events: All Randomized Subjects

Group	Subject	Preferred Term	Severity	Trial Day of Onset [Day Postdose]
NB16	054-NB-301-032	Infection	Severe	27 [22]
	086-NB-301-040*	Acute myocardial infarction	Severe	49 [36]
	094-NB-301-075	Ovarian fibroma	Moderate	411 [25]
NB32	092-NB-301-022	Colon cancer	Severe	423 [30]
	015-NB-302-006	Gallbladder cancer	Severe	65 [48]
	034-NB-302-028	Back pain	Severe	368 [303]
	034-NB-302-046	Cholecystitis	Severe	402 [8]
	037-NB-302-054	Atrial flutter	Severe	36 [15]
	066-NB-303-054	Renal cell carcinoma	Moderate	315 [17]
	066-NB-303-109	Hyperthyroidism	Severe	75 [31]
	071-NB-304-015	Postoperative wound infection	Moderate	118 [22]
Placebo	094-NB-301-003	Renal neoplasm	Severe	483 [90]
	060-NB-304-015	Deep vein thrombosis	Mild	314 [28]

Table includes serious adverse events occurring >7 days from last confirmed dose. Highlighting indicates events within 30 day window from last dose.

*The Acute Myocardial Infarction case is of concern due to the imbalance of MIs in the NB vs Placebo groups. This subject discontinued due to his AE of GERD prior to the SAE of acute MI. Additional information on this individual is provided in Appendix C1.

6.3.3 Dropouts and/or Discontinuations

Primary Dataset:
In the double-blind treatment phase, 23.8% of subjects receiving NB and 11.9% of subjects receiving placebo discontinued treatment due to an AE[23]. The most common (≥1% in any group) AEs leading to discontinuation were nausea, headache, dizziness, and vomiting. All these events were reported at a higher incidence in the Total NB group compared with placebo. For nausea, headache and vomiting, the incidence increases with dose. In addition, hypertension and palpitations each led to discontinuation in 0.3% of Total NB subjects and none were reported in placebo subjects.

Table 29: Treatment-Emergent Adverse Events (≥0.5% in Any Group) Leading to Treatment Discontinuation: Primary Dataset, Double-Blind Treatment Phase

Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)	NB vs Placebo p-value
Double-Blind Treatment Phase					
Subjects discontinuing treatment due to any AE	**181 (11.9%)**	**139 (22.0%)**	**612 (24.0%)**	**771 (23.8%)**	**<.001**
Nausea	3 (0.2%)	32 (5.1%)	160 (6.3%)	203 (6.3%)	<.001
Headache	9 (0.6%)	10 (1.6%)	43 (1.7%)	55 (1.7%)	.002
Dizziness	5 (0.3%)	15 (2.4%)	23 (0.9%)	42 (1.3%)	.001
Vomiting	1 (<0.1%)	4 (0.6%)	28 (1.1%)	35 (1.1%)	<.001
Insomnia	7 (0.5%)	5 (0.8%)	17 (0.7%)	23 (0.7%)	0.290
Anxiety	10 (0.7%)	1 (0.2%)	19 (0.7%)	21 (0.6%)	0.843
Urticaria	4 (0.3%)	3 (0.5%)	16 (0.6%)	19 (0.6%)	0.198
Depression	13 (0.9%)	6 (0.9%)	10 (0.4%)	16 (0.5%)	0.144
Blood pressure increased	3 (0.2%)	3 (0.5%)	10 (0.4%)	13 (0.4%)	0.276
Rash	2 (0.1%)	1 (0.2%)	12 (0.5%)	13 (0.4%)	0.125
Hypertension	0	3 (0.5%)	7 (0.3%)	11 (0.3%)	0.021
Fatigue	3 (0.2%)	3 (0.5%)	7 (0.3%)	10 (0.3%)	0.518
Palpitations	0	5 (0.8%)	4 (0.2%)	10 (0.3%)	0.031
Abdominal pain	1 (<0.1%)	5 (0.8%)	4 (0.2%)	9 (0.3%)	0.157
Tremor	1 (<0.1%)	3 (0.5%)	6 (0.2%)	9 (0.3%)	0.141

Data Source: Applicant's Table ISS.P.6.3-3.1.
Includes only AEs with 'drug stopped (primary)' as the reason for treatment discontinuation.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48; AE=adverse event.

Less frequent AEs (<1% and at least 3 times the incidence of placebo) that led to treatment discontinuation in the Total NB group but rarely in the placebo group were constipation, disturbance in attention, rash, abdominal pain, diarrhea, and tremor.

23 In Orexigen's Advisory Committee briefing document they report the incidence of patients discontinuing treatment due to an AE as 27.8% for Total NB and 15.9% for placebo. These calculations are based on the number of patients with adverse events as the denominator for each treatment group. The percentages in the FDA briefing document used the total number of patients in the primary safety analysis set in each treatment as the denominator.

Table 30: Less Frequent Adverse Events Leading to Treatment Discontinuation in Total NB: Primary Dataset, Double-Blind Treatment Phase

Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)	NB vs Placebo p-value
Constipation	1 (<0.1%)	2 (0.3%)	11 (0.4%)	13 (0.4%)	0.044
Disturbance in attention	1 (<0.1%)	2 (0.3%)	11 (0.4%)	13 (0.4%)	0.064
Rash	2 (0.1%)	1 (0.2%)	12 (0.5%)	13 (0.4%)	0.125
Abdominal pain	1 (<0.1%)	5 (0.8%)	4 (0.2%)	9 (0.3%)	0.157
Diarrhea	1 (<0.1%)	1 (0.2%)	7 (0.3%)	9 (0.3%)	0.136
Tremor	1 (<0.1%)	3 (0.5%)	6 (0.2%)	9 (0.3%)	0.141
Feeling jittery	0	0	6 (0.2%)	7 (0.2%)	0.085
Hot flush	0	2 (0.3%)	5 (0.2%)	7 (0.2%)	0.070
Somnolence	0	1 (0.2%)	6 (0.2%)	7 (0.2%)	0.062
Vertigo	0	2 (0.3%)	5 (0.2%)	7 (0.2%)	0.067

Data Source: Applicant's Table ISS.P.6.3-3.1.
Includes only AEs with 'drug stopped (primary)' as the reason for treatment discontinuation.
Adverse events were coded using MedDRA 12.0.
Frequencies are analyzed using Cochran-Mantel-Haenszel (CMH) general association test controlling for study.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48; AE=adverse event.

Subgroup Analysis for gender, age, and race

Common AEs leading to discontinuation are those that occurred in ≥1% of subjects in any treatment group during the double-blind treatment phase, which includes nausea, headache, dizziness and vomiting.

Gender:
Subjects were predominantly female in both the Total NB and placebo groups. In the Total NB group, females had a higher overall incidence of AEs leading to discontinuation compared with males (25.2% vs. 16.9%, respectively); the incidence was similar between females and males in the placebo group (12.0% vs. 11.6%, respectively). Common AEs leading to discontinuation that occurred at a higher incidence in females compared with males in the Total NB group were nausea (7.0% vs. 2.6%), vomiting (1.2% vs. 0.7%), and dizziness (1.4% vs. 0.7%). In the placebo group, similar trends were observed for nausea and vomiting, whereas dizziness occurred at a lower incidence in females compared with males (0.2% vs. 0.7%, respectively).

Age:
Subjects were predominantly between 18 and 64 years of age in both the Total NB and placebo groups. Due to the small number of subjects ≥65 years old (32 subjects in the placebo group and 62 subjects in the Total NB group), comparisons with the ≥65 years old category are limited. Within the placebo group, the overall incidence of AEs leading to discontinuation was similar across the age groups: 18-44: 11.4%; 45-64: 12.4%; ≥ 65: 12.5%. Within the NB group, AEs leading to discontinuation were higher in the >65 age group as compared to the other age groups: 18-44: 21.2%; 45-64: 25.4%; ≥ 65: 38.7%. AEs leading to discontinuation were higher in the NB group as compared to the placebo group across all age groups.

Race: Subjects were predominantly White in both the Total NB and placebo groups. In the Total NB group, the incidence of AEs leading to discontinuation was somewhat higher in 'Other' (non-White or non-Black/African American) and Blacks/African-Americans compared with Whites (31.8%, 27.5%, vs. 22.4%, respectively). In the placebo group, the incidence was higher in 'Other' compared with Blacks/African Americans and Whites (18.0% vs. 10.7% and 11.9%, respectively. Across race subgroups, AEs leading to discontinuation were higher in the NB group as compared to the placebo group.

Comparison of Diabetic and Nondiabetic Datasets
In the double-blind treatment phase, 29.4% of subjects receiving NB32 and 15.4% of subjects in the placebo group in the Diabetic Dataset discontinued treatment due to an AE, incidences that were slightly higher than the incidences seen in the NB32 group (23.2%) and placebo group (11.6%) in the Nondiabetic Dataset. The most common (≥1% in any group) AEs leading to discontinuation were nausea, vomiting, headache, depression, diabetes mellitus, and hyperglycemia. In the NB32 group, a higher percentage of subjects who had diabetes discontinued treatment due to nausea and vomiting than subjects who did not have diabetes (9.6% vs. 5.8% and 3.0% vs. 0.8%, respectively); the same trend was not observed in the placebo group. The incidence of discontinuation for depression, diabetes mellitus, and hyperglycemia was higher in the placebo group than in the Total NB group in both the Diabetic and Nondiabetic Datasets.

Table 31: Most Common (≥1% in Any Group) Adverse Events Leading to Treatment Discontinuation: Diabetic and Nondiabetic Datasets, Double-Blind Treatment Phase

Preferred Term	Nondiabetic Dataset		Diabetic Dataset	
	Placebo (N=1346) n (%)	NB32 (N=2212) n (%)	Placebo (N=169) n (%)	NB32 (N=333) n (%)
Subjects discontinuing treatment due to any AE	**156 (11.6%)**	**514 (23.2%)**	**26 (15.4%)**	**98 (29.4%)**
Nausea	3 (0.2%)	128 (5.8%)	0	32 (9.6%)
Vomiting	1 (<0.1%)	18 (0.8%)	0	10 (3.0%)
Headache	9 (0.7%)	37 (1.7%)	0	6 (1.8%)
Depression	10 (0.7%)	8 (0.4%)	3 (1.8%)	2 (0.6%)
Diabetes Mellitus	2 (0.1%)	0	2 (1.2%)	1 (0.3%)
Hyperglycemia	0	0	2 (1.2%)	0

Data Source: Applicant's Table ISS.S.6.3-3.1 and Table 14.3-11A in Trial NB-304 CSR
Includes only AEs with 'drug stopped (primary)' as the reason for treatment discontinuation.
For the Diabetic Dataset, the preferred term diabetes mellitus denoted worsening of diabetes mellitus.
Abbreviations: AE=adverse event.

6.3.4 Submission Specific Primary Safety Concerns

Treatment-emergent adverse events of special interest (see list below) were summarized by MedDRA Queries. Orexigen's method of categorizing the adverse events of special interest is as follows:

- The Special Topic categories comprise all preferred terms present in the database which had been prespecified, along with relevant additional terms needed to fully describe the medical concept.

The special topics predefined in the ISS Statistical Analysis Plan and a listing of all preferred terms found in the integrated database were used as a starting point for identifying the preferred terms to be included in each category. The composition of each Special Topic, including assignment to subtopic and category, was reviewed by two physicians. Where a Standardized MedDRA Query (SMQ) was prespecified, all terms in the SMQ were compared against the listing of all preferred terms in the database; only terms present in the database were included. A given preferred term could appear in more than one category if the symptom was a potential component of more than one disease (i.e., "crying" was added to both the Potential Depression Symptoms and Potential Mood Disorders subgroups, both are categories within Psychiatric Disorders). In such a case, the preferred term would be counted once in each category, but only once in the overall Special Topic and/or Subtopic. All preferred terms were updated to the MedDRA version 12.0.

Vital sign and laboratory data are discussed along with the relevant special topics:

1. Blood Pressure and Pulse
2. Cardiovascular Events
3. Seizure and Convulsions
4. Suicide-related Events
5. Psychiatric Events
6. Cognitive Disorders
7. Renal Function
8. Liver and Gallbladder
9. Hypersensitivity Reaction/Skin Rash

6.3.4.1. Blood Pressure and Pulse

Blood pressure and pulse rate were measured in the sitting position at every trial visit. In Phase 3 trials, the value used for analyses was an average of three blood pressure and pulse readings obtained after the subject had been sitting for at least 5 minutes to minimize the effects of variability associated with measurement of blood pressure and pulse rate.

Hypertension

Blood pressure measurements are of special interest in obese populations. Overweight individuals have a three-fold increased risk for the development of hypertension compared to normal-weight individuals. The prevalence of hypertension among the obese approaches 50%.[24,25] The prevalence of hypertension in the NB primary dataset was 24%.

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[26] the relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney disease. For individuals

24 Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. JAMA. 1978;240:1607-1610.
25 Rexrode KM, Manson JE, Hennekens CH. Obesity and cardiovascular disease. Curr Opin Cardiol. 1996;11:490-495.
26 JNC7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf

40–70 years of age, each increment of 20 mmHg in systolic BP (SBP) or 10 mmHg in diastolic BP (DBP) doubles the risk of CVD across the entire BP range from 115/75 to 185/115 mmHg. Furthermore, even modest increases in blood pressure and pulse are associated with an elevated risk of cardiovascular events.[27,28]

The hypertension subtopic includes the following preferred terms: Hypertension, blood pressure increased, ECG signs of ventricular hypertrophy, labile hypertension, blood pressure diastolic increased, blood pressure systolic increased, and cardiovascular disorder.

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). The majority of the events were reported within the Hypertension subtopic (5.3% Total NB and 4.0% placebo). No Blood Pressure or Pulse-related SAEs were reported in the Primary datasets. Discontinuation of treatment due to a Blood Pressure- or Pulse-related TEAE was higher in the Total NB group compared with the placebo group (0.8% and 0.3%, respectively). The majority of discontinuations were attributable to the Hypertension category.

Table 32: Incidence of Blood Pressure and Pulse-Related Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Blood Pressure Subtopic	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Double-Blind Treatment Phase				
Subjects with Any Blood Pressure and Pulse-Related TEAE	**64 (4.2%)**	**29 (4.6%)**	**161 (6.3%)**	**192 (5.9%)**
Hypertension	60 (4.0%)	22 (3.5%)	149 (5.9%)	173 (5.3%)
Hypotension	0	0	1 (<0.1%)	1 (<0.1%)
Bradycardia	1 (<0.1%)	3 (0.5%)	1 (<0.1%)	4 (0.1%)
Tachycardia	3 (0.2%)	4 (0.6%)	17 (0.7%)	21 (0.6%)
Subjects with any SAE	**0**	**0**	**0**	**0**
Subjects discontinued due to AE	**4 (0.3%)**	**7 (1.1%)**	**17 (0.7%)**	**25 (0.8%)**
Hypertension	3 (0.2%)	6 (0.9%)	17 (0.7%)	25 (0.8%)
Hypotension	0	0	0	0
Bradycardia	1 (<0.1%)	0	0	0
Tachycardia	0	1 (0.2%)	0	1 (<0.1%)

Data Source: Applicant's Table ISS. P.BP.1-1, ISS.P.BP.2-1, and ISS.P.BP.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Time to Onset and Duration of Hypertension Events: Among the subjects who reported hypertension TEAEs, initial onset was observed in 45% of subjects within the first 12 weeks in the Total NB group and 30% of subjects within the first 12 weeks in the Placebo group. Median

27 Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001;345:1291-1297
28 Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 2010;159:612-619

time to onset was 14 and 25.5 weeks for Total NB and placebo, respectively. The median duration of hypertension events was 6 weeks in the Total NB group compared to 5 weeks for the placebo group.

Table 33: Time-to-Onset and Duration of Treatment-Emergent Adverse Events-Hypertension: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)	Total NB (N=3239)
Subjects with any TEAE-Hypertension, n	**60**	**173**
Time-to-onset (weeks)		
>0 to 4 weeks	2 (3.3%)	25 (14.5%)
>4 to 8 weeks	10 (16.7%)	29 (16.8%)
>8 to 12 weeks	6 (10.0%)	23 (13.3%)
>12 to 16 weeks	6 (10.0%)	13 (7.5%)
>16 to 20 weeks	1 (1.7%)	9 (5.2%)
>20 to 24 weeks	3 (5.0%)	10 (5.8%)
>24 to 28 weeks	6 (10.0%)	13 (7.5%)
>28 to 32 weeks	3 (5.0%)	9 (5.2%)
>32 to 36 weeks	3 (5.0%)	8 (4.6%)
>36 to 40 weeks	2 (3.3%)	10 (5.8%)
>40 to 44 weeks	4 (6.7%)	7 (4.0%)
>44 to 48 weeks	7 (11.7%)	4 (2.3%)
>48 to 52 weeks	2 (3.3%)	7 (4.0%)
>52 to 56 weeks	3 (5.0%)	5 (2.9%)
>56 weeks	2 (3.3%)	1 (0.6%)
Mean (SD)	26.5 (17.1)	20.0 (15.9)
Median	25.5	14.0
Duration (weeks)		
Mean (SD)	12.2 (13.6)	12.7 (13.9)
Median	5.0	6.0

Data Source: Orexigen's Table ISS.P.BP.1-5.
Treatment-emergent AEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation]).
The time-to-onset of the specified AE will be calculated (in days) as the difference between the start date of the AE and the date of the first dose of study treatment +1 day.
The duration of the specified AE (i.e., only those events that are presented in the time to AEs) is defined as the difference between the stop date and the start date of the AE + 1 day.
Week Calculation = ceiling (stop date of the AE - start date of the AE + 1 day) / 7)
Abbreviations: TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment.

Hypertension TEAEs by Gender, Age, and Race: Events of hypertension were reported with disproportionate frequency for males vs. females compared to the distribution of the enrolled population for both Placebo and NB populations. Eighteen percent of the Placebo population is male but 32% experienced a hypertension TEAE; 17% of the Total NB population is male but

30% experienced a hypertension TEAE. Hypertension events for both NB-treated and placebo subjects were also disproportionately represented among subjects aged 45-64 years versus younger subjects (53% of the Placebo population is 45-64 years but 63% experienced a hypertension TEAE; 54% of the Total NB population is 45-64 years but 67% experienced a hypertension TEAE). Among the subjects experiencing hypertension events, a greater proportion were Black/African American in the NB-treated group (26.0%) compared to the placebo-treated group (11.7%).

Six NB-treated subjects experienced a Hypertension event rated by the investigator as severe compared to zero placebo subjects. Among subjects in both treatment groups with hypertension events, few had two or more consecutive recorded systolic blood pressures (or last visit value) ≥160 mm Hg (2, 1.2% Total NB: 1, 1.7% placebo) but more NB subjects had consecutive increases in systolic blood pressures (or last visit value) ≥140 mm Hg (57, 33% Total NB: 17, 28% placebo). Similarly, there were slightly more NB subjects who experienced two or more consecutive recorded diastolic blood pressures (or last visit value) ≥100 mm Hg compared to placebo (8, 4.6% Total NB: 2, 3.3% placebo) or ≥90 mm Hg (42, 24% Total NB: 12, 20% placebo).

Among subjects experiencing a TEAE of hypertension, a similar percentage of subjects who required treatment (defined as new or increased dose of antihypertensive medication) was seen between treatment groups, (40% Total NB, 43% placebo). The proportion of subjects with hypertension TEAE who had resolution of the event without requiring antihypertensive therapy was also similar (31% Total NB, 35% placebo).

Systolic Blood Pressure Analysis

At Weeks 4 and 8, mean systolic blood pressure showed initial increases from baseline of +0.96 and +1.18 mm Hg, respectively, for NB 16 and +0.73 and +0.66 mm Hg, respectively for NB32. Over the same time period, the Placebo group experienced mean systolic decreases at Weeks 4 and 8 of -1.58 and -1.57mm Hg, respectively. 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.

At trial-end in the Total NB group, mean SBP was at or slightly below baseline. In the placebo group, mean systolic blood pressure was consistently decreased from baseline over time, reaching a maximum change at Week 28 of -2.84 mm Hg. Beyond Week 28, the approximate mean change from baseline averaged -2.2 mm Hg in the Placebo group.

Table 34: Systolic Blood Pressure (mm Hg), Change from Baseline by Visit Safety Analysis Set, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Week	N	Treatment	n	Baseline Mean (mm Hg)	Change in Mean	Difference from Placebo (mm Hg)	p-value (vs. placebo)
Week 4	4208	Placebo	1414	119	-1.58		
		NB16	531	119	0.96		
		NB32	2214	119	0.73		
		Total NB	2794	119	0.80	2.39	<.001
Week 8	3663	Placebo	1282	119	-1.57		

Week	N	Treatment	n	Baseline Mean (mm Hg)	Change in Mean	Difference from Placebo (mm Hg)	p-value (vs. placebo)
		NB16	456	119	1.18		
		NB32	1885	119	0.66		
		Total NB	2381	119	0.83	2.40	<.001
Week 12	3401	Placebo	1174	119	-1.87		
		NB16	417	120	0.61		
		NB32	1774	119	-0.21		
		Total NB	2227	119	-0.01	1.82	<.001
Week 24	3047	Placebo	1018	119	-2.83		
		NB16	382	120	-0.79		
		NB32	1617	119	-1.47		
		Total NB	2029	119	-1.24	1.57	<.001
Week 52	2409	Placebo	779	120	-2.35		
		NB16	283	120	-0.68		
		NB32	1347	119	-0.82		
		Total NB	1630	119	-0.79	1.52	<.001
Week 56	2339	Placebo	751	120	-2.33		
		NB16	276	120	-0.24		
		NB32	1312	119	-0.94		
		Total NB	1588	119	-0.82	1.54	<.001

Source: Derived from Orexigen's Table ISS.P.8.2-2
Red font color signifies blood pressure increases
1) The safety analysis set includes all randomized subjects who are administered at least one tablet 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.
(2) Results are based on observed values for subjects completing their assessments at each visit while within 7 days of last confirmed dose date.
(3) NB vs. placebo p-value for NB pooled treatment group vs. placebo: Type III sums of squares from ANCOVA model: Treatment, Study and Baseline.

The mean change from baseline to endpoint in systolic blood pressure was -1.6 mm Hg for placebo and -0.3 mm Hg for Total NB. The mean change from baseline to maximum systolic blood pressure increased by 7 mm Hg for placebo and 9 mm Hg for Total NB.

The table below demonstrates that:

- In general, a greater percentage of Placebo subjects experienced systolic blood pressure shifts <90 mm Hg as compared to NB subjects.
- In general, a greater percentage of NB subjects experienced systolic blood pressure increases in the range of ≥140 to <160 mm Hg (JNC7 Stage 1 Hypertension).
- In general, a greater percentage of NB subjects experienced systolic blood pressure increases in the range of ≥160 mm Hg (JNC7 Stage 2 Hypertension)—especially in the first 16 weeks.

Table 35: Systolic Blood Pressure (mm Hg) Shift Table from Baseline to Trial Visit for Subjects with a Normal Baseline Value (90-<140 mm Hg): Primary Dataset, Double-Blind Treatment Phase

	Placebo				Total NB			
SBP	<90 n (%)	Normal ≥90-<140 n (%)	≥140-<160 n (%)	≥160 n (%)	<90 n (%)	Normal ≥90-<140 n (%)	≥140-<160 n (%)	≥160 n (%)
Week 4	2 (0.1%)	1368 (96.7%)	28 (2.0%)	0	6 (0.2%)	2647 (94.7%)	100 (3.6%)	4 (0.1%)
Week 8	3 (0.2%)	1243 (97.0%)	22 (1.7%)	0	2 (<0.1%)	2253 (94.6%)	94 (3.9%)	1 (<0.1%)
Week 12	2 (0.2%)	1134 (96.6%)	24 (2.0%)	0	3 (0.1%)	2123 (95.3%)	72 (3.2%)	3 (0.1%)
Week 16	5 (0.4%)	1077 (96.4%)	22 (2.0%)	0	6 (0.3%)	2020 (95.3%)	66 (3.1%)	4 (0.2%)
Week 20	5 (0.5%)	1015 (96.1%)	20 (1.9%)	3 (0.3%)	2 (<0.1%)	1990 (96.0%)	57 (2.8%)	1 (<0.1%)
Week 24	5 (0.5%)	980 (96.3%)	22 (2.2%)	0	2 (<0.1%)	1950 (96.1%)	55 (2.7%)	1 (<0.1%)
Week 28	4 (0.4%)	861 (95.9%)	22 (2.4%)	1 (0.1%)	8 (0.4%)	1770 (96.1%)	39 (2.1%)	3 (0.2%)
Week 32	2 (0.2%)	835 (96.2%)	20 (2.3%)	1 (0.1%)	2 (0.1%)	1719 (96.5%)	41 (2.3%)	0
Week 36	2 (0.2%)	808 (96.1%)	20 (2.4%)	1 (0.1%)	3 (0.2%)	1677 (95.9%)	48 (2.7%)	2 (0.1%)
Week 40	3 (0.4%)	785 (96.4%)	16 (2.0%)	1 (0.1%)	4 (0.2%)	1642 (95.9%)	46 (2.7%)	2 (0.1%)
Week 44	4 (0.5%)	761 (95.1%)	24 (3.0%)	1 (0.1%)	1 (<0.1%)	1631 (96.0%)	46 (2.7%)	2 (0.1%)
Week 48	3 (0.4%)	752 (95.9%)	18 (2.3%)	1 (0.1%)	2 (0.1%)	1582 (96.1%)	39 (2.4%)	4 (0.2%)
Week 52	5 (0.6%)	748 (96.0%)	15 (1.9%)	1 (0.1%)	2 (0.1%)	1562 (95.8%)	42 (2.6%)	5 (0.3%)
Week 56	0	725 (96.5%)	16 (2.1%)	0	6 (0.4%)	1509 (95.0%)	51 (3.2%)	3 (0.2%)

Data Source: Orexigen's Table Table 26Jul2010-12.1
Abbreviation: SBP=systolic blood pressure; Total NB=all doses of combination naltrexone and bupropion treatment.
JNC7 Stage 1 (systolic) HTN: 140-159 mm Hg
JNC7 Stage 2 (systolic) HTN: ≥ 160 mm Hg

Outlier systolic blood pressure values were evaluated through prespecified analyses of single and/or multiple increases above baseline (≥10 and ≥15 mm Hg), increases above threshold (≥150 or ≥160 mm Hg at two consecutive assessments or at the final visit), and shifts to potentially clinically significant values (<85 or >150 mm Hg). The incidences of systolic blood pressure increases above prespecified thresholds were higher in the Total NB group than the placebo group. Subjects in the Total NB group were 2.5 times as likely to experience two or more SBP readings ≥150 mm Hg [41 (1.5%) NB vs 9 (0.6%) Placebo] and were 2x as likely to experience 2 or more SBP readings ≥160 mm Hg [5 (0.2%) NB vs 2 (0.1%) Placebo].

Table 36: Incidence of Treatment-Emergent Increases in Systolic Blood Pressure: Primary Dataset, Double-Blind Treatment Phase

Category	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Subjects with ≥ 1 post-BL measurement	**1419**	**2812**
≥2 values ≥140 mm Hg	56 (3.9%)	180 (6.4%)
≥2 values ≥150 mm Hg[a]	9 (0.6%)	41 (1.5%)
≥2 values ≥160 mm Hg[a]	2 (0.1%)	5 (0.2%)

≥2 values ≥10 mm Hg over BL[b]	264 (18.6%)	703 (25.0%)
≥2 values ≥15 mm Hg over BL[b]	112 (7.9%)	301 (10.7%)
≥1 value ≥10 mm Hg over BL	515 (36.3%)	1226 (43.6%)
≥1 value ≥15 mm Hg over BL	261 (18.4%)	648 (23.0%)

Data Source: Orexigen's Table ISS.P.8.2-4.
a At least two consecutive treatment-emergent values or a single treatment-emergent value if last (subjects with a value ≥150 or ≥160 mm Hg at baseline are excluded from the analysis).
b At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
Results are based on values observed within 7 days of last confirmed dose.
Abbreviations: BL=baseline; Total NB=all doses of combination naltrexone and bupropion treatment.

Diastolic Blood Pressure Analysis

At Weeks 4 and 8, mean diastolic blood pressure showed initial increases from baseline of +1.31 and +1.38 mm Hg, respectively, for NB 16 and +0.64 and +0.52 mm Hg, respectively for NB32. Over the same time period, the Placebo group experienced mean diastolic decreases at Weeks 4 and 8 of -1.18 and -1.39 mm Hg, respectively. 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 difference from placebo was 0.5 mm Hg, which was not statistically significant.

Table 37: Diastolic Blood Pressure (mm Hg), Change from Baseline by Visit Safety Analysis Set, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Week	N	Treatment	n	Baseline Mean (mm Hg)	Change in Mean	Difference from Placebo (mm Hg)	p-value (vs. placebo)
Week 4	4208	Placebo	1414	77	-1.18		
		NB16	531	76	1.31		
		NB32	2214	77	0.64		
		Total NB	2794	77	0.74	1.90	<.001
Week 8	3663	Placebo	1282	77	-1.39		
		NB16	456	76	1.38		
		NB32	1885	77	0.52		
		Total NB	2381	77	0.72	2.05	<.001
Week 12	3401	Placebo	1174	77	-1.75		
		NB16	417	77	0.79		
		NB32	1774	77	-0.25		
		Total NB	2227	77	-0.06	1.65	<.001
Week 24	3047	Placebo	1018	77	-2.12		
		NB16	382	76	-0.33		
		NB32	1617	77	-1.06		
		Total NB	2029	77	-0.91	1.22	<.001
Week 52	2409	Placebo	779	77	-2.16		
		NB16	283	76	-0.36		
		NB32	1347	77	-1.24		
		Total NB	1630	77	-1.09	1.08	<.001
Week 56	2339	Placebo	751	77	-1.50		
		NB16	276	76	-0.37		
		NB32	1312	77	-1.14		
		Total NB	1588	77	-1.01	0.51	.078

Source: Derived from Orexigen's Table ISS.P.8.1-2

Week	N	Treatment	n	Baseline Mean (mm Hg)	Change in Mean	Difference from Placebo (mm Hg)	p-value (vs. placebo)
Red font color signifies blood pressure increases 1) The safety analysis set includes all randomized subjects who are administered at least one tablet 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 trial. (2) Results are based on observed values for subjects completing their assessments at each visit while within 7 days of last confirmed dose date. (3) NB vs. placebo p-value for NB pooled treatment group vs. placebo: Type III sums of squares from ANCOVA model: Treatment, Study and Baseline.							

By trial-end, mean diastolic blood pressure in the Total NB group was generally maintained at approximately 1 mm Hg below baseline. In contrast, the placebo group showed a consistent decrease in mean diastolic blood pressure across monthly timepoints of approximately 2 mm Hg below baseline.

The mean change from baseline to endpoint in diastolic blood pressure was -1.3 mm Hg for placebo and -0.5 mm Hg for Total NB. Mean change from baseline to maximum in diastolic blood pressure increased by 4.8 mm Hg for placebo and 5.9 mm Hg for Total NB.

Outlier diastolic blood pressure values were evaluated through prespecified analyses of single and/or multiple increases above baseline (≥5, ≥10 and ≥20 mm Hg), increases above threshold (two consecutive assessments or the final visit ≥95 or ≥100 mm Hg), and shifts to potentially clinically significant values (PCS) (<50 or >95 mm Hg). Incidences of diastolic blood pressure increases above threshold (≥95 and ≥100 mm Hg) and single and/or multiple increases ≥ 5, 10, or 20 mm Hg above baseline were more frequent in the Total NB group.

Table 38: Incidence of Treatment-Emergent Increases in Diastolic Blood Pressure: Primary Dataset, Double-Blind Treatment Phase

Category	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Subjects with ≥ 1 post-BL measurement	**1419**	**2812**
≥2 values ≥90 mm Hg	64 (4.5%)	180 (6.4%)
≥2 values ≥95 mm Hg[a]	23 (1.6%)	56 (2.0 %)
≥2 values ≥100 mm Hg[a]	6 (0.4%)	12 (0.4%)
≥2 values ≥5 mm Hg over BL[b]	406 (28.6%)	1039 (36.9%)
≥2 values ≥10 mm Hg over BL[b]	141 (9.9%)	374 (13.3%)
≥1 value ≥10 mm Hg over BL	282 (19.9%)	768 (27.3%)
≥1 value ≥20 mm Hg over BL	38 (2.7%)	88 (3.1%)

Data Source: Orexigen's Table ISS.P.8.1-4.
a At least two consecutive treatment-emergent values or a single treatment-emergent value if last (subjects with a value ≥95 or ≥100 mm Hg at baseline are excluded from the analysis).
b At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
Results are based on values observed within 7 days of last confirmed dose.
Abbreviations: BL=baseline; Total NB=all doses of combination naltrexone and bupropion treatment.

The table below demonstrates that:

- Throughout the trial, in general, more Placebo subjects experienced diastolic blood pressure shifts <60 mm Hg as compared to NB subjects.
- At every time point, a greater percentage of Placebo subjects had a normal diastolic blood pressure as compared to NB subjects
- For the first 32 weeks, a greater number of NB subjects experienced diastolic blood pressure increases in the range of ≥90 to <100 mm Hg (JNC7 Stage 1 Hypertension). After 32 weeks, the percentages were similar.
- The percentage of subjects who experienced diastolic blood pressure increases in the range of ≥100 mm Hg (JNC7 Stage 2 Hypertension) was similar between the two treatment groups.

Table 39: Diastolic Blood Pressure (mm Hg) Shift Table from Baseline to Trial Visit for Subjects with a Normal Baseline Value (60-<90 mm Hg): Primary Dataset, Double-Blind Treatment Phase

	Placebo				Total NB			
DBP	<60 n (%)	Normal ≥60-<90 n (%)	≥90-<100 n (%)	≥100 n (%)	<60 n (%)	Normal ≥60-<90 n (%)	≥90-<100 n (%)	≥100 n (%)
Week 4	13 (0.9%)	1342 (94.9%)	30 (2.1%)	2 (0.1%)	20 (0.7%)	2569 (91.9%)	112 (4.0%)	2 (<0.1%)
Week 8	14 (1.1%)	1215 (94.8%)	28 (2.2%)	0	11 (0.5%)	2201 (92.4%)	84 (3.5%)	8 (0.3%)
Week 12	19 (1.6%)	1110 (94.5%)	22 (1.9%)	1 (<0.1%)	16 (0.7%)	2052 (92.1%)	83 (3.7%)	5 (0.2%)
Week 16	15 (1.3%)	1051 (94.1%)	28 (2.5%)	0	21 (1.0%)	1958 (92.4%)	66 (3.1%)	8 (0.4%)
Week 20	10 (0.9%)	1007 (95.4%)	15 (1.4%)	2 (0.2%)	21 (1.0%)	1926 (93.0%)	55 (2.7%)	5 (0.2%)
Week 24	26 (2.6%)	952 (93.5%)	20 (2.0%)	0	22 (1.1%)	1890 (93.1%)	53 (2.6%)	1 (<0.1%)
Week 28	10 (1.1%)	839 (93.4%)	29 (3.2%)	2 (0.2%)	18 (1.0%)	1693 (92.0%)	65 (3.5%)	1 (<0.1%)
Week 32	10 (1.2%)	817 (94.1%)	23 (2.6%)	2 (0.2%)	18 (1.0%)	1643 (92.2%)	58 (3.3%)	3 (0.2%)
Week 36	10 (1.2%)	788 (93.7%)	23 (2.7%)	3 (0.4%)	15 (0.9%)	1631 (93.3%)	45 (2.6%)	2 (0.1%)
Week 40	16 (2.0%)	758 (93.1%)	23 (2.8%)	1 (0.1%)	20 (1.2%)	1580 (92.2%)	55 (3.2%)	3 (0.2%)
Week 44	12 (1.5%)	748 (93.5%)	22 (2.8%)	3 (0.4%)	19 (1.1%)	1578 (92.9%)	46 (2.7%)	3 (0.2%)
Week 48	8 (1.0%)	733 (93.5%)	26 (3.3%)	1 (0.1%)	22 (1.3%)	1519 (92.3%)	52 (3.2%)	2 (0.1%)
Week 52	18 (2.3%)	728 (93.5%)	17 (2.2%)	1 (0.1%)	20 (1.2%)	1508 (92.5%)	48 (2.9%)	4 (0.2%)
Week 56	9 (1.2%)	704 (93.7%)	23 (3.1%)	1 (0.1%)	16 (1.0%)	1480 (93.2%)	40 (2.5%)	3 (0.2%)

Data Source: Orexigen's Table 26Jul2010-11.1
Abbreviation: DBP=diastolic blood pressure; Total NB=all doses of combination naltrexone and bupropion treatment.
JNC7 Stage 1 (diastolic) HTN: 90-99 mm Hg
JNC7 Stage 2 (diastolic) HTN: ≥ 100 mm Hg

Hypotension

There was a single event in the Primary dataset within the Hypotension subtopic, an NB32 subject with orthostatic hypotension. An additional two NB-treated subjects experienced such events in the Overall dataset (one additional event of orthostatic hypotension and one event of blood pressure decreased). No event within this subtopic was serious or led to study drug discontinuation.

Bradycardia
Within the Bradycardia subtopic, TEAEs were uncommon (≤0.1% for placebo and Total NB), with three NB-treated subjects experiencing events with preferred terms of sinus bradycardia and a placebo subject with bradycardia in the Primary Dataset. No event within this subtopic was serious or led to study drug discontinuation.

Tachycardia
Within the Tachycardia subtopic, TEAEs were more frequent for Total NB subjects (0.6%) than for placebo (0.2%). No SAEs were reported for any subject within the Tachycardia subtopic, and there were no events judged by the investigator to be severe. One event in an NB16 subject (Subject 11-NB-201-022) led to study drug discontinuation.

No subjects in the Placebo or Total NB group experienced a TEAE of tachycardia along with 2 or more consecutive elevations of SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg. Time to onset analysis for Tachycardia events did not appear to shown any marked predilection for early onset for NB. The events tended to be of short duration for both treatment groups (median duration 1.0 week for Total NB and placebo; mean duration 5 weeks for NB and 1 week for Placebo). However maximum duration was 2 weeks for Placebo compared to 32 weeks for NB.

Pulse Rate Analysis
At Weeks 4 and 8, mean pulse rate showed initial increases from baseline of +2.47 and +3.05 bpm, respectively, for NB 16 and +1.85 and +2.45 bpm, respectively for NB32. Over the same time period, the Placebo group experienced a mean pulse rate decrease at Week 4 of -0.21 and mean pulse rate increase of 0.43 bpm. At both Weeks 4 and 8, the Total NB group had a statistically significant difference from placebo of +2.1 bpm. By Week 52, the statistically significant difference from placebo was +1.7 bpm.

Table 40: Pulse Rate (bpm), Change from Baseline by Visit, Safety Analysis Set, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Week	N	Treatment	n	Baseline Mean (bpm)	Change in Mean	Difference from Placebo (bpm)	p-value (vs. placebo)
Week 4	4208	Placebo	1414	72	-0.21		
		NB16	531	71	2.47		
		NB32	2214	72	1.85		
		Total NB	2794	71	1.95	2.08	<.001
Week 8	3663	Placebo	1282	71	0.43		
		NB16	456	71	3.05		
		NB32	1885	71	2.45		
		Total NB	2381	71	2.58	2.14	<.001
Week 12	3401	Placebo	1174	71	0.20		
		NB16	417	71	3.19		
		NB32	1774	72	2.34		
		Total NB	2227	71	2.51	2.35	<.001
Week 24	3047	Placebo	1018	72	0.64		
		NB16	382	71	2.27		

Week	N	Treatment	n	Baseline Mean (bpm)	Change in Mean	Difference from Placebo (bpm)	p-value (vs. placebo)
		NB32	1617	71	1.84		
		Total NB	2029	71	1.89	1.29	<.001
Week 52	2409	Placebo	779	71	-0.63		
		NB16	283	71	3.58		
		NB32	1347	72	2.03		
		Total NB	1630	72	2.30	1.72	<.001
Week 56	2409	Placebo	751	71	-0.98		
		NB16	276	71	1.30		
		NB32	1312	72	0.09		
		Total NB	1588	72	0.30	1.35	<.001

Source: Derived from Orexigen's Table ISS.P.8.3-2
Red font color signifies blood pressure increases
1) The safety analysis set includes all randomized subjects who are administered at least one tablet 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 trial.
(2) Results are based on observed values for subjects completing their assessments at each visit while within 7 days of last confirmed dose date.
(3) NB vs. placebo p-value for NB pooled treatment group vs. placebo: Type III sums of squares from ANCOVA model: Treatment, Study and Baseline.

The mean change from baseline to endpoint in pulse was -0.2 in Placebo and + 1 bpm in Total NB. The mean change from baseline to maximum in pulse increased by 7.8 bpm for placebo and 9.1 bpm for Total NB.

Outlier pulse values were evaluated through prespecified analyses of single and/or multiple increases above baseline (≥5, ≥10, ≥20, and ≥50 bpm), increase above threshold (two consecutive assessments or the final visit ≥90 bpm), and shifts to potentially clinically significant values (pulse <45 or >110). The incidence of pulse increases ≥90 bpm at two consecutive or the final visit was seen in 4.9% of the Total NB group and 4.4% of the placebo group. Increases in pulse from baseline (≥5, ≥10, and ≥20 bpm) were observed at higher incidences in NB-treated subjects. A ≥50 bpm increase in pulse was seen in one subject in the placebo group.

Table 41: Incidence of Treatment-Emergent Increases in Pulse: Primary Dataset, Double-Blind Treatment Phase

Category	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Subjects with ≥ 1 post-BL measurement	**1419**	**2812**
≥2 values ≥90 bpm[a]	62 (4.4%)	137 (4.9 %)
≥2 values ≥100 bpm	7 (0.5%)	27 (1.0%)
≥2 values ≥5 bpm over BL[b]	609 (42.9%)	1484 (52.8%)
≥2 values ≥10 bpm over BL[b]	269 (19.0%)	741 (26.4%)
≥1 value ≥10 bpm over BL	538 (37.9%)	1290 (45.9%)
≥1 value ≥20 bpm over BL	123 (8.7%)	304 (10.8%)
≥1 value ≥50bpm over BL	1 (<0.1%)	0

Data Source: Orexigen's Table ISS.P.8.3-4.
a At least two consecutive treatment-emergent values or a single treatment-emergent value if last (subjects with a value of

≥90 bpm at baseline are excluded from the analysis).
b At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
Results are based on values observed within 7 days of last confirmed dose.
Abbreviations: BL=baseline; Total NB=all doses of combination naltrexone and bupropion treatment.

The table below demonstrates that throughout the trial, more Placebo subjects experienced pulse rate shifts to values <60 bpm as compared to NB subjects. While there were few subjects in the NB or the Placebo group who experienced pulse rates ≥110 bpm, a greater number of NB subjects—particularly in the first 32 weeks of the trial— experienced pulse rate increases to values in the range of ≥100 to <110 bpm.

Table 42: Pulse Rate (bpm) Shift Table from Baseline to Trial Visit for Subjects with a Normal Baseline Value (60-99 bpm): Primary Dataset, Double-Blind Treatment Phase

	Placebo				Total NB			
Pulse	<60 n (%)	Normal ≥60-<100 n (%)	≥100-<110 n (%)	≥110 n (%)	<60 n (%)	Normal ≥60-<100 n (%)	≥100-<110 n (%)	≥110 n (%)
Week 4	59 (4.2%)	1274 (90.1%)	1 (<0.1%)	0	83 (3.0%)	2527 (90.4%)	15 (0.5%)	1 (<0.1%)
Week 8	50 (3.9%)	1153 (89.9%)	1 (<0.1%)	0	53 (2.2%)	2168 (91.1%)	18 (0.8%)	1 (<0.1%)
Week 12	38 (3.2%)	1060 (90.3%)	4 (0.3%)	1 (<0.1%)	37 (1.7%)	2043 (91.7%)	13 (0.6%)	0
Week 16	50 (4.5%)	995 (89.1%)	3 (0.3%)	1 (<0.1%)	48 (2.3%)	1935 (91.3%)	12 (0.6%)	0
Week 20	41 (3.9%)	941 (89.1%)	7 (0.7%)	1 (<0.1%)	57 (2.8%)	1880 (90.7%)	10 (0.5%)	0
Week 24	50 (4.9%)	904 (88.8%)	1 (<0.1%)	0	54 (2.7%)	1843 (90.8%)	11 (0.5%)	2 (<0.1%)
Week 28	46 (5.1%)	795 (88.5%)	0	0	66 (3.6%)	1660 (90.2%)	5 (0.3%)	0
Week 32	28 (3.2%)	780 (89.9%)	3 (0.3%)	0	50 (2.8%)	1611 (90.4%)	11 (0.6%)	0
Week 36	27 (3.2%)	755 (89.8%)	4 (0.5%)	0	40 (2.3%)	1591 (91.0%)	8 (0.5%)	1 (<0.1%)
Week 40	27 (3.3%)	728 (89.4%)	4 (0.5%)	1 (0.1%)	45 (2.6%)	1557 (90.9%)	7 (0.4%)	0
Week 44	31 (3.9%)	710 (88.8%)	4 (0.5%)	0	45 (2.6%)	1542 (90.8%)	9 (0.5%)	0
Week 48	26 (3.3%)	702 (89.5%)	3 (0.4%)	0	42 (2.6%)	1495 (90.8%)	7 (0.4%)	0
Week 52	28 (3.6%)	698 (89.6%)	1 (0.1%)	0	34 (2.1%)	1488 (91.3%)	10 (0.6%)	0
Week 56	42 (5.6%)	657 (87.5%)	0	0	56 (3.5%)	1426 (89.8%)	4 (0.3%)	0

Data Source: Orexigen's Table 26Jul2010-10.1
Abbreviation: Total NB=all doses of combination naltrexone and bupropion treatment.

Analyses of Weight Loss and Change in Vital Signs (diastolic blood pressure, systolic blood pressure, pulse, and pressure-rate product)

These analyses were performed in both the Full Analysis dataset and the Completers dataset. The patterns were similar in both populations but the Completers analyses is more informative as it

compares subjects from NB and placebo groups who completed the trial and is unaffected by drop-outs during the trial.

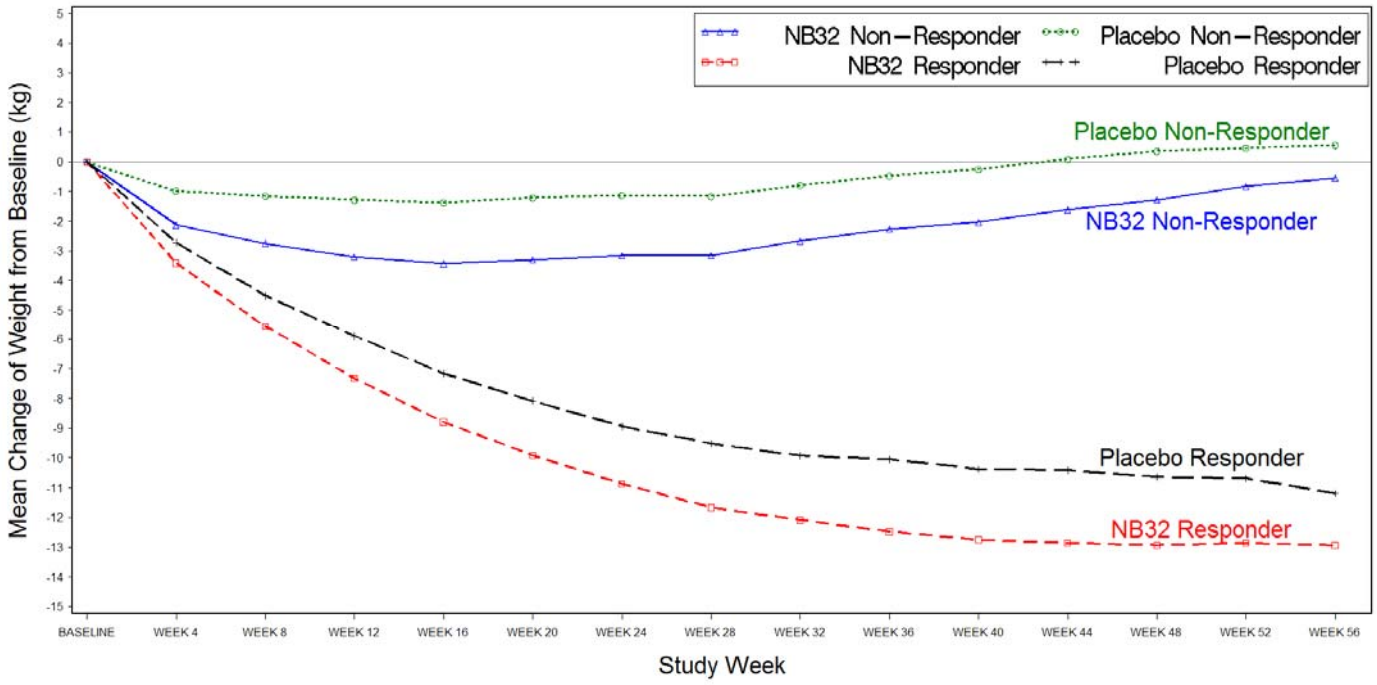
In the applicant's ISS, the Completers Population was defined as the following:

- For trials NB-301, NB-303, and NB-304, the Completers Population included all randomized subjects with a baseline measurement, a post baseline body weight measurement, and who completed 56 weeks of treatment.
- For Trial NB-302, the Completers Population included all randomized subjects who had a baseline measurement and a post-baseline measurement at Week 56 while on study drug (i.e. active treatment).

By definition, the Completers Population was a subset of the Full Analysis Set. Among the 3,833 patients in the Full Analysis Set, a total of 2,357 patients were completers. Among the 2,357, a total of 2,073 patients were randomized to receive placebo or NB-32.

The figure below shows the mean change in weight (in kg) by drug and responder group. The responder group for this analysis was defined as subjects with a ≥ 5% decrease in body weight.

Figure 5: Change of Weight by Treatment Response Group (≥ 5% decrease in body weight, Completers Population)

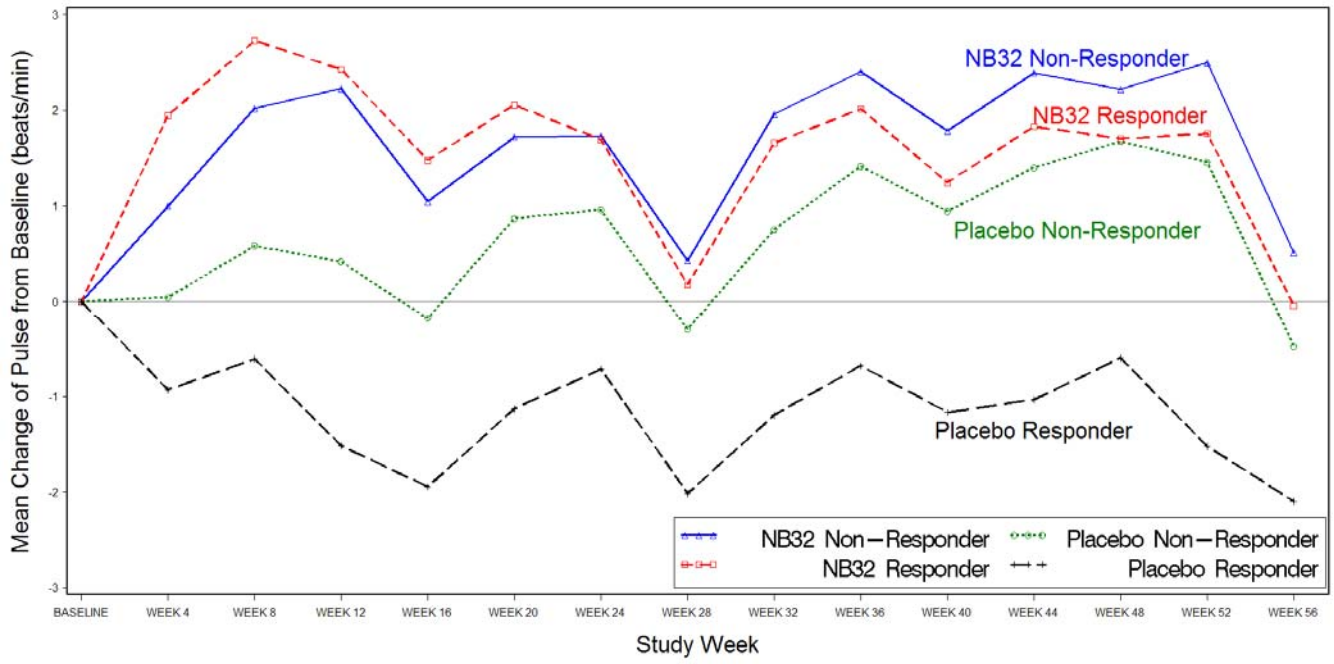


Source: Figure courtesy of FDA Statistical Reviewer Xiao Ding

The figure below shows change in pulse by drug and responder groups. The Placebo Responder group had the most beneficial change in pulse throughout the trial. The NB32 Responder and Non-Responder groups had an immediate increase in pulse. After Week 24, the NB32 Non-

Responder group has the most unfavorable pulse response. For the Total NB group (responder and non-responder groups combined) across monthly timepoints from Week 4 through Week 56, mean heart rate was increased above baseline by ~1-3 bpm (range of means: 0.3 bpm to 2.5 bpm). Thus, subjects randomized to NB experienced a small but chronic increase in heart rate throughout the duration of the trial.

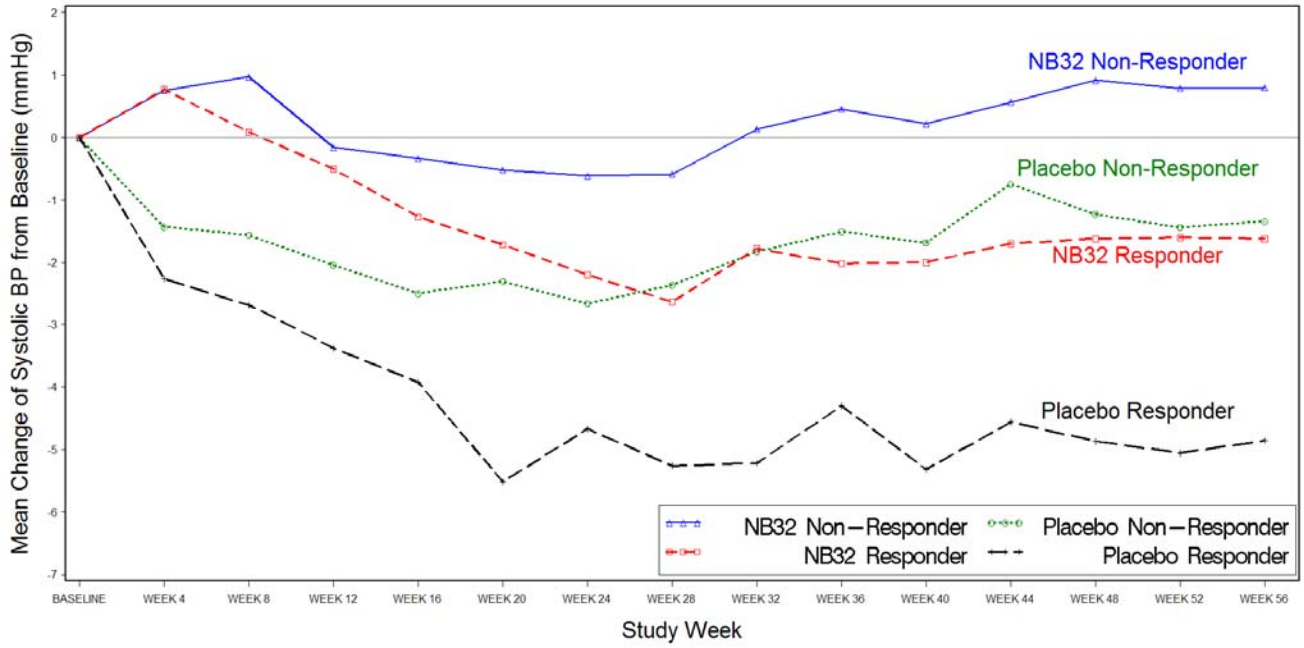
Figure 6: Change of Pulse (bpm) by Treatment Response Group (≥ 5% decrease in body weight, Completers Population)



Source: Figure courtesy of FDA Statistical Reviewer Xiao Ding

The figure below looks at SBP by drug and responder group. Clearly the Placebo Responders had the most favorable SBP changes while the NB32 Non-Responders had the most unfavorable SBP changes.

Figure 7: Change of Systolic Blood Pressure by Treatment Response Group (≥ 5% decrease in body weight, Completers Population)



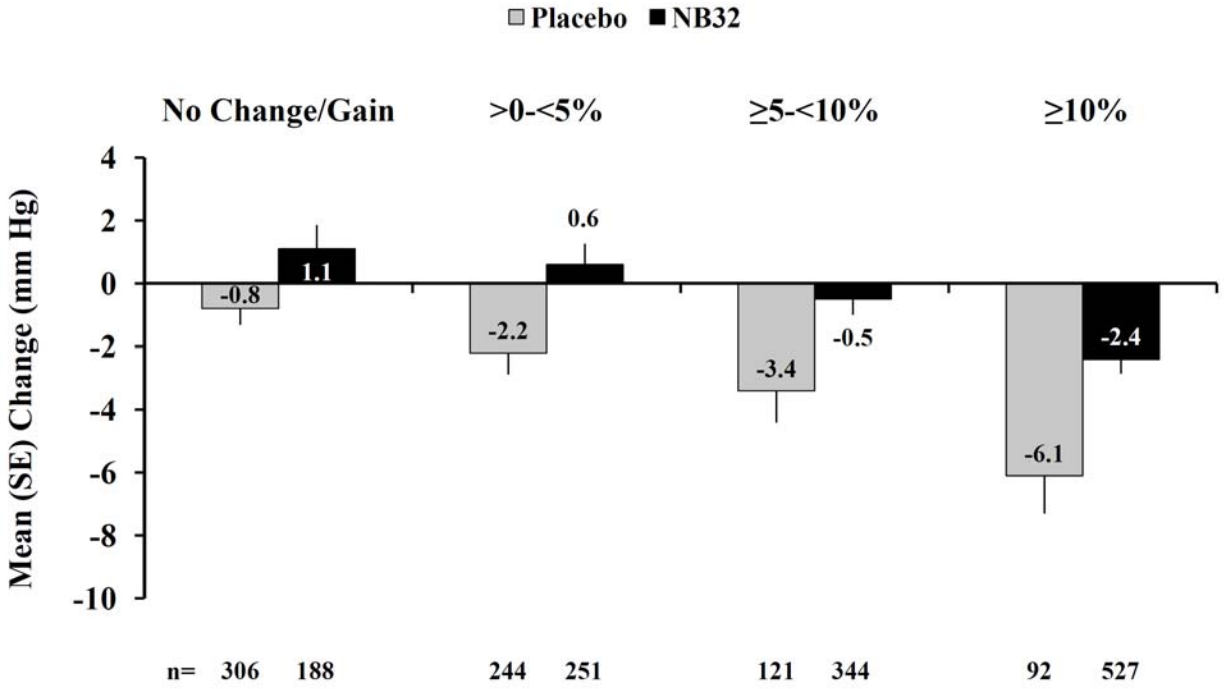
Source: Figure courtesy of FDA Statistical Reviewer Xiao Ding

Orexigen was asked to submit 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.

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 (Figure 6), 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 ≥ 10% weight loss (-2.4 mm Hg). 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.

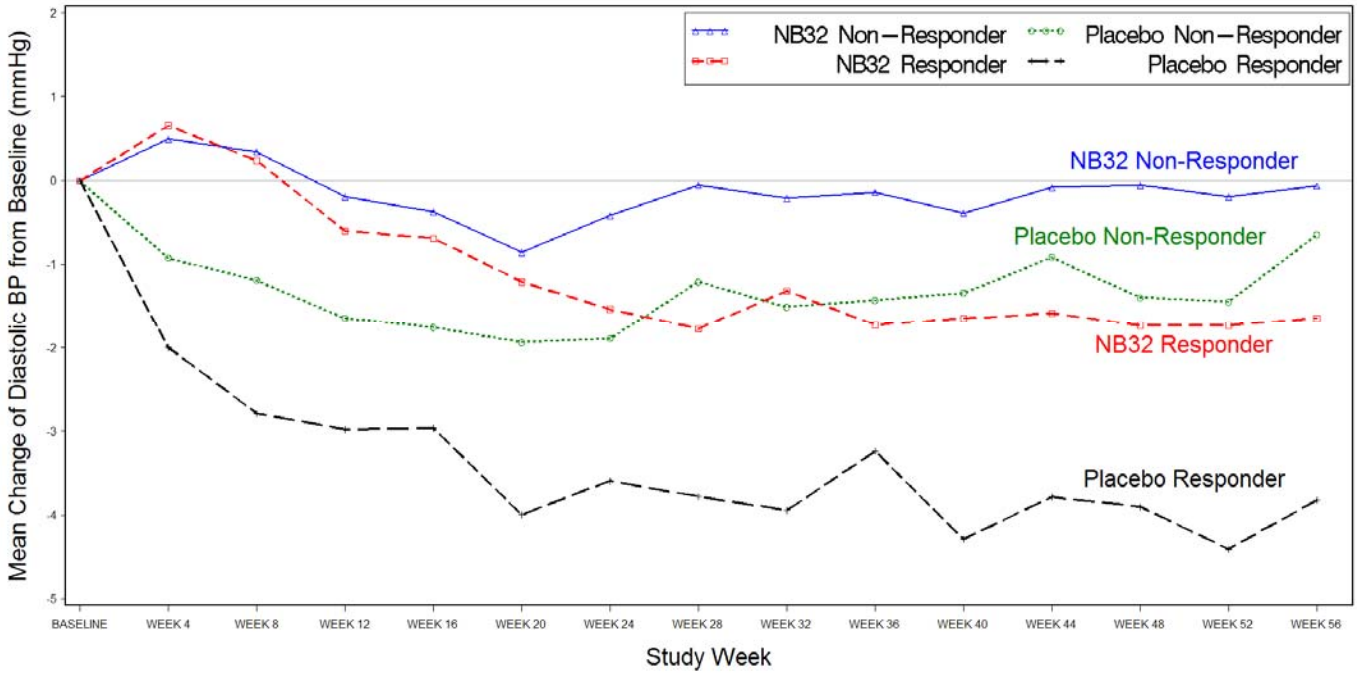
Figure 8: Change in SBP at Endpoint by Endpoint Body Weight Change (Completers)



Source: Orexigen Figure 27Sep2010 – 1.3.4

Figure 9 looks at DBP by drug and responder group (≥ 5% decrease in body weight). Similar to the SBP changes seen in Figure 7, the Placebo Responders had the most favorable DBP changes while the NB32 Non-Responders had the most unfavorable DBP changes.

Figure 9: Change of Diastolic Blood Pressure by Treatment Response Group (≥ 5% decrease in body weight, Completers Population)

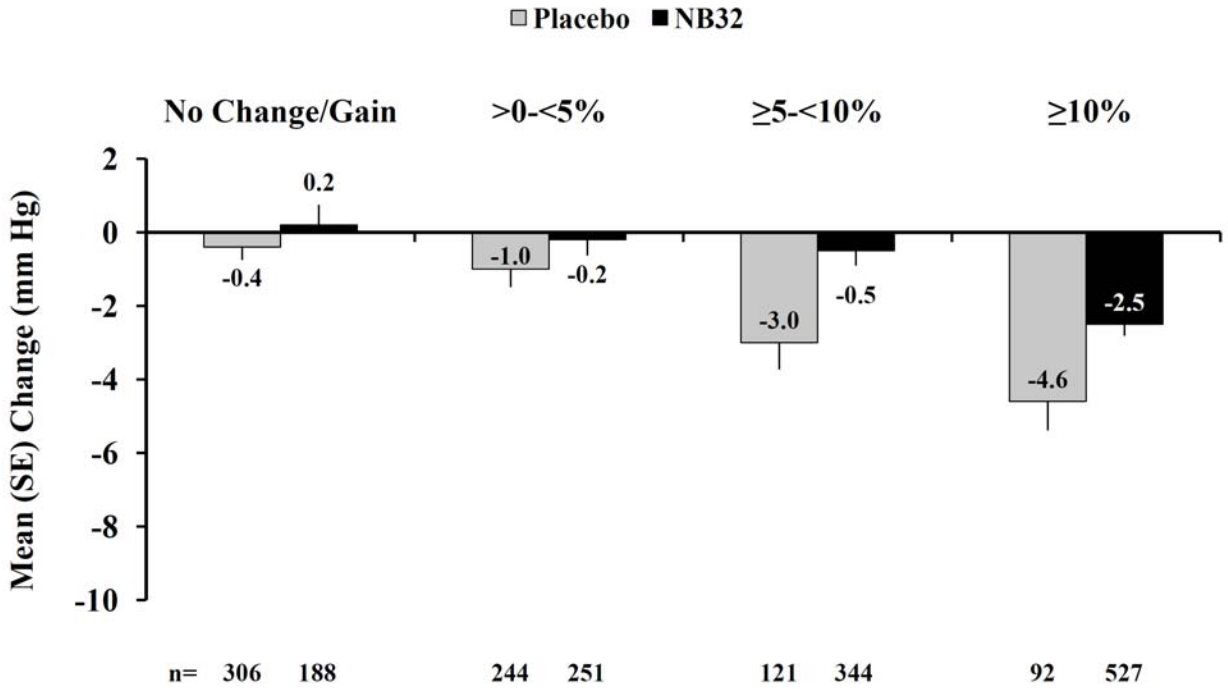


Source: Figure courtesy of FDA Statistical Reviewer Xiao Ding

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, when looking at the Responder analysis of NB subjects who lost at least 5% of their initial body weight (Figure 9), reductions from baseline in mean diastolic blood pressure were seen. However, this Responder Analysis by four weight change categories shows that subjects do not achieve a meaningful decrease in DBP until they have lost ≥ 10% weight loss (-2.5 mm Hg). 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.

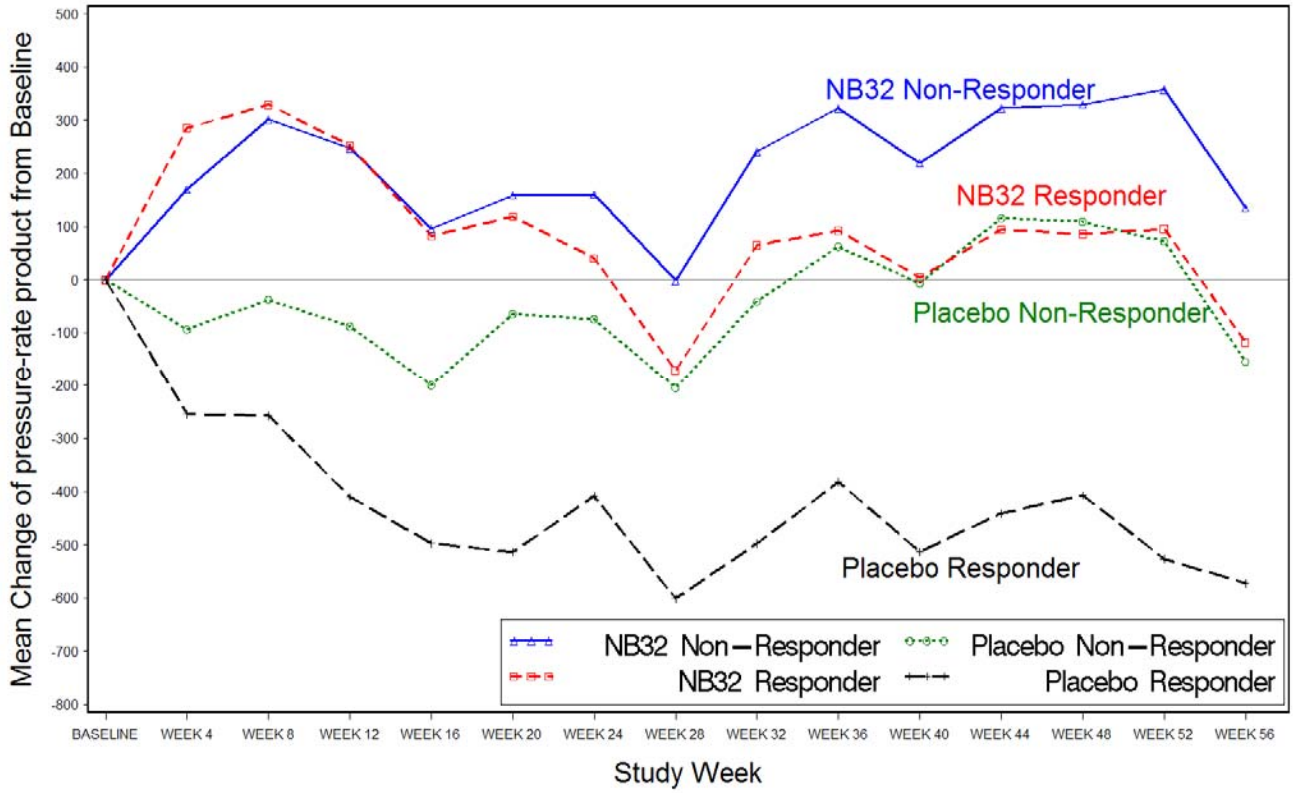
Figure 10: Change in DBP at Endpoint by Endpoint Body Weight Change (Completers)



Source: Orexigen Figure 27Sep2010 – 1.3.6

The figure below looks at the pressure-rate product by drug and treatment responder group. The pressure-rate product (heart rate x systolic blood pressure) correlates with myocardial oxygen consumption. Again, the Placebo Responders had the most favorable pressure-rate product while the NB32 Non-Responders had the most unfavorable changes. The pressure-rate product generally tended to be increased relative to baseline throughout the course of treatment with NB32 and decreased relative to baseline for placebo.

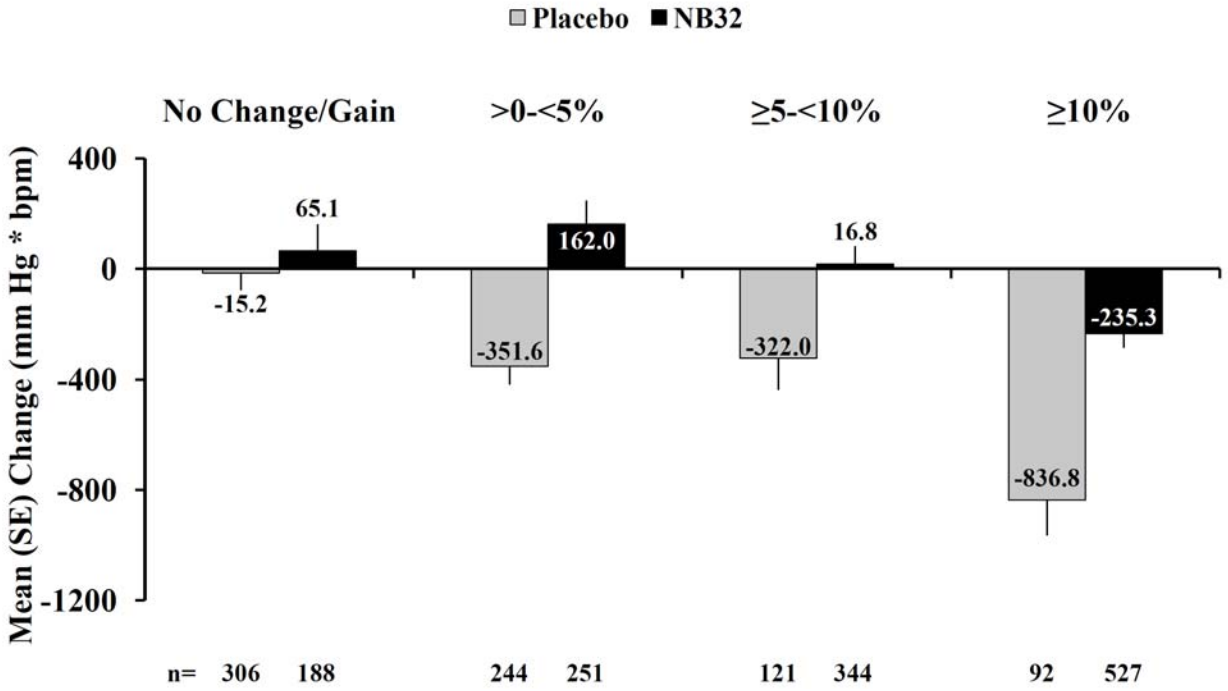
Figure 11: Change of Pressure-Rate Product by Treatment Response Group (≥ 5% decrease in body weight, Completers Population)



Source: Figure courtesy of FDA Statistical Reviewer Xiao Ding

The bar graph below shows the changes from baseline to endpoint for Pressure Rate Product for each weight response category in the Completer's Dataset. Again, placebo subjects, regardless if they gain or lose weight, experience a decrease in Pressure Rate Product. In contrast, only the NB32 subjects that lose 10% or more of body weight (40% of NB32 completers), experience any decrease in Pressure Rate Product as compared to 100% of Placebo completers.

Figure 12: Change in Pressure Rate Product at Endpoint by Endpoint Body Weight Change (Completers)



Source: Orexigen Figure 27Sep2010 – 1.3.10

Table 43: Summary of Change of Vital Sign from Baseline to Week 56 by Treatment Response Group (≥ 5% decrease in body weight, Completers Population)

Treatment Group	**Change of Diastolic Blood Pressure (mm Hg)** Mean (SD) Median (Range)	**Change of Systolic Blood Pressure (mm Hg)** Mean (SD) Median (Range)	**Change of Pulse (bpm)** Mean (SD) Median (Range)	**Change of Pressure-Rate Product** Mean (SD) Median (Range)
NB-32 Non-responder (N=439)	-0.06 (6.99) 0 (-28, 21)	0.80 (10.44) 0 (-58, 39)	0.51 (7.97) 1 (-27, 31)	134.90 (1323) 80 (-4759, 7945)
Placebo Non-responder (N=551)	-0.65 (6.87) -1 (-24, 38)	-1.34 (9.88) -1 (-35, 33)	-0.47 (7.12) 0 (-26, 20)	-154.50 (1103) -130 (-4619, 3098)
NB-32 Responder (N=871)	-1.65 (7.20) -2 (-30, 32)	-1.61 (9.74) -2 (-35, 32)	-0.04 (7.65) 0 (-31, 32)	-118.14 (1163) -167 (-3745, 4692)
Placebo Responder (N=212)	-3.82 (7.78) -3 (-29, 28)	-4.85 (11.24) -4 (-43, 43)	-2.09 (7.78) -2 (-23, 27)	-571.63 (1263) -569.5 (-4063, 3773)

Source: Table courtesy of FDA Statistical Reviewer Xiao Ding

Table 44: Summary of Change of Vital Sign from Baseline to Week 56 by Treatment Response Group (≥ 5% decrease in body weight, Full Analysis Set)

Treatment Group	Change of Diastolic Blood Pressure (mm Hg) Mean (SD) Median (Range)	Change of Systolic Blood Pressure (mm Hg) Mean (SD) Median (Range)	Change of Pulse (bpm) Mean (SD) Median (Range)	Change of Pressure-Rate Product Mean (SD) Median (Range)
NB-32 Non-responder (N=957)	0.39 (7.00) 0 (-28, 22)	1.01 (10.07) 1 (-58, 39)	1.19 (8.18) 1 (-53, 31)	222.40 (1288) 187 (-5163, 7945)
Placebo Non-responder (N=1046)	-0.51 (6.85) -1 (-24, 38)	-0.85 (9.38) -1 (-35, 40)	0.09 (7.48) 0 (-33, 27)	-54.62 (1127) -67.5 (-4619, 5054)
NB-32 Responder (N=1085)	-1.44 (7.23) -1 (-30, 32)	-1.34 (9.96) -2 (-35, 32)	0.36 (7.63) 0 (-31, 32)	-51.68 (1176) -93 (-3745, 4692)
Placebo Responder (N=273)	-3.48 (7.68) -3 (-29, 28)	-4.86 (10.93) -4 (-43, 43)	-1.63 (8.02) -2 (-24, 31)	-520.15 (1258) -549 (-4063, 3773)

Source: Table courtesy of FDA Statistical Reviewer Xiao Ding

Ambulatory Blood Pressure

Ambulatory blood pressure monitoring (ABPM) provides information about BP during daily activities and sleep. The ambulatory BP values are usually lower than clinic readings. According to the literature, individuals with hypertension generally have an average BP of more than 135/85 mmHg while awake and more than 120/75 mmHg during sleep. The level of BP measurement by using ABPM correlates better than office measurements with target organ injury[29] and cardiovascular events.[30] ABPM also provides a measure of the percentage of BP readings that are elevated, the overall BP load, and the extent of BP reduction during sleep. In most individuals, BP decreases by 10 to 20 percent during the night; those in whom such reductions are not present are at increased risk for cardiovascular events.[31] Fagard et. al. performed a meta-analysis on individual data of 3468 patients from 4 prospective studies performed in Europe. Age of the subjects averaged 61±13 years, 45% were men, 13.7% smoked, 8.4% had diabetes, and 61% were under antihypertensive treatment at the time of ambulatory blood pressure monitoring. One of the main findings of the meta-analysis of individual patient data on the prognostic significance of ABP (systolic) in hypertensive patients without major cardiovascular disease at baseline was that daytime and nighttime ABP significantly predicted all-cause and CV mortality, CHD, stroke and an aggregate of major CVD, independently from

29 Verdecchia P. Prognostic value of ambulatory blood pressure: current evidence and clinical implications. *Hypertension.* 2000;35:844-51

30 Staessen J, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. JAMA. 1999;282:539-546.

31 JNC7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and treatment of High Blood Pressure
http://www nhlbi nih.gov/guidelines/hypertension/express.pdf

office blood pressure and confounding factors. Only nighttime ABP predicted noncardiovascular mortality.[32]

Blood pressure load is an integrated measure of the 24-hour blood pressure that is correlated with end-organ damage[33]. It is defined as the proportion of 24-hour blood pressure recordings that are increased (higher than 135/85 mm Hg over the 24 hours) relative to the thresholds for waking and sleep blood pressure (usually higher than 140/90 mm Hg during the awake period and higher than 125/80 mm Hg during the sleep hours)[34].

A substudy of NB-303 examined average 24-hour ambulatory blood pressure monitoring parameters which included average daytime (7:00 A.M.-10:00 P.M) and night-time (10:00 P.M.-7:00 A.M) blood pressure in overweight and obese subjects (N=180) treated for up to 56 weeks with naltrexone plus bupropion combination therapy (n=121) or with placebo (n=59). The primary objective of this sub-study was to evaluate the change from baseline to endpoint (Week 52) in average 24-hour ABPM systolic and diastolic blood pressure. These measures were obtained at baseline (prior to administration of study drug), Week 24, and endpoint (Week 52). The LS mean change and summary statistics for the baseline to endpoint analyses in average 24-hour ABPM systolic and diastolic blood pressures are provided in Table 45. The secondary objectives of this sub-study were to evaluate the change from baseline in average daytime (7:00 A.M.-10:00 P.M) and average nighttime (10:00 P.M.-7:00 A.M) systolic and diastolic blood pressure and to evaluate the change from baseline in 24-hour blood pressure load (defined as percentage of both systolic >135 mm Hg and diastolic >85 mm Hg over 24 hours).

There were 182 individuals enrolled from nine sites from the parent trial NB-303 and 117 were included in the primary analyses. Of the randomized sub-study subjects, 112 (61.5%) completed the trial to Week 52. In the sub-study, 62.3% of the 122 subjects randomized to NB32/48 and 60.0% of the 60 subjects randomized to placebo completed the trial. The number of subjects who discontinued the trial in the NB32/48 was 37.7% (46/122) and 40.0% for the placebo group (24/60) and was comparable. The most common reason for early termination of the trial was adverse events which accounted for 21.3% (26/122) in the NB32/48 group and 11.7% (7/60; p=0.112) in the placebo group.

For the sub-study analysis set overall, the mean weight was 98.33 kg and mean BMI was 36.06 kg/m^2 and the majority of subjects (42.2%) had a BMI that was between ≥ 30 kg/m^2 and <35 kg/m^2. Overall, 9.4% of total sub-study subjects reported current tobacco use (9.1% for NB32/48 and 10.2% for placebo). The percentage of subjects in the NB32/48 and placebo groups of the sub-study with hypertension (27.3% vs 28.8%) and dyslipidemia (51.2% vs 55.9%) were similar between groups.

32 Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension. 2008 Jan;51(1):55-61.
33 McGrath BP. Ambulatory blood pressure monitoring. Med J Aust. 2002;176(12):588-592.
34 Wurdeman RL, Mooss AN, Mohiuddin SM, Lucas BD Jr, Ryschon KL, Hilleman DE.
Comparison of 24-hour ambulatory blood pressure data in hypertensive patients switched from nifedipine-GITS to nifedipine-CC. Pharmacotherapy. 1999;19(1):94-100.

Subjects in the NB32/48 group experienced a greater LS mean weight change compared to the placebo group at endpoint (Week 52; decrease of 7.49% vs 2.62%) and the difference was -4.88% (95% CI [-7.24, -2.51]; p≤0.001).

Average 24-hour ABPM Systolic and Diastolic Blood Pressure

At baseline, the means of the average 24-hour ABPM systolic and diastolic blood pressures were similar between the NB32/48 group (121.24 mm Hg and 72.93 mm Hg, respectively) and the placebo group (121.96 mm Hg and 73.38 mm Hg, respectively). At baseline, the maximums of the average 24-hour ambulatory systolic and diastolic blood pressures for NB32/48 were 141.11 mm Hg and 89.12 mm Hg, respectively, and for placebo were 141.43 mm Hg and 89.30 mm Hg, respectively.

At endpoint (Week 52), the LS mean change in systolic blood pressure was -0.21 mm Hg for NB32/48 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).**

Table 45: Average 24-Hour ABPM Systolic and Diastolic Blood Pressure (mm Hg) LS Mean Change and Descriptive Statistics from Baseline to Endpoint: ABPM Sub-study Analysis Set (Trial NB-303 ABPM)

	Baseline		Endpoint		Change from Baseline				
	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum	LS Mean (SE)	Diff (95% CI)	p-value
Systolic blood pressure (mm Hg)									
Placebo (N=38)	122.0 (9.4)	102.6, 141.4	119.4 (10.5)	102.5, 142.3	-2.6 (7.1)	-19.4, 13.1	-2.8 (1.3)		
NB32/48 (N=79)	121.2 (8.9)	105.1, 141.1	121.01 (10.0)	94.4, 143.4	-0.2 (7.6)	-19.5, 21.5	-0.2 (0.9)	2.6 (-0.3,5.6)	0.081
Diastolic blood pressure (mm Hg)									
Placebo (N=38)	73.4 (8.0)	58.3, 89.3	71.5 (7.6)	59.4, 85.8	-1.9 (3.8)	-8.5, 5.5	-2.1 (0.9)		
NB32/48 (N=79)	72.9 (6.9)	57.1, 89.1	73.8 (7.3)	51.3, 89.2	0.9 (5.6)	-16.5, 20.3	0.8 (0.6)	2.9 (0.9, 4.8)	0.004

Source: Orexigen's Section 14, Table 14.3-6 and Table 14.3-7
Abbreviations: CI = confidence interval; Diff = least squares mean difference; LS = least squares; mm Hg = millimeters of mercury; N = number of subjects per group; NB32/48 = pooled group of subjects received either naltrexone SR 32/bupropion SR 360 or naltrexone SR 48/bupropion SR 360; SD = standard deviation; SE = standard error.
Notes: *Sub-study analysis set* includes all subjects who were randomized in the sub-study, had a baseline ABPM measurement, were administered at least one tablet of study treatment, and had at least one investigator contact/assessment after the start of study treatment.
Endpoint is the last available data while on study medication (last observation carried forward analyses).
p-values are based on type III sums of squares from the ANCOVA model that included treatment and pooled study center as main effects, with the baseline blood pressure as a covariate.

Analyses for LS mean change from baseline to Week 24 revealed similar treatment differences. The LS mean change in systolic blood pressure for NB32/48 was -1.04 mm Hg and for placebo was -3.90 mm Hg. **The treatment difference was 2.87 mm Hg (95% CI [-0.18, 5.91]; p=0.064).**

The LS mean change in diastolic blood pressure was 1.27 mm Hg for the NB32/48 group and -1.75 mm Hg for the placebo group with a **treatment difference between the NB32/48 and placebo groups of 3.03 mm Hg (95% CI [0.66, 5.40]; p=0.013)**.

Table 46: Average 24-Hour ABPM Systolic and Diastolic Blood Pressure (mm Hg) LS Mean Change and Descriptive Statistics from Baseline to Week 24: ABPM Sub-study Analysis Set (Trial NB-303 ABPM)

	Baseline		Week 24		Change from Baseline				
	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum	LS Mean (SE)	Diff (95% CI)	p-value
Systolic blood pressure (mm Hg)									
Placebo (N=26)	120.7 (9.3)	102.6, 141.4	116.9 (9.3)	97.0, 134.9	-3.8 (5.7)	-18.8, 8.8	-3.9 (1.4)		
NB32/48 (N=63)	120.6 (8.9)	105.1, 141.1	119.7 (9.5)	94.4, 141.1	-0.9 (6.7)	-16.0, 16.2	-1.0 (1.0)	2.9 (-0.2,5.9)	0.064
Diastolic blood pressure (mm Hg)									
Placebo (N=26)	73.5 (8.7)	58.3, 89.3	71.4 (7.4)	57.1, 85.2	-2.1 (4.0)	-11.4, 5.8	-1.8 (1.1)		
NB32/48 (N=63)	72.8 (6.6)	60.7, 89.1	74.0 (7.1)	51.2, 89.2	1.2 (5.6)	-12.2, 15.3	1.3 (0.8)	3.0 (0.7, 5.4)	0.013

Source: Orexigen's Section 14, Table 14.3-8 and Table 14.3-9
Abbreviations: CI = confidence interval; Diff = least squares mean difference; LS = least squares mean; mm Hg = millimeters of mercury; N = number of subjects per group; NB32/48 = pooled group of subjects received either naltrexone SR 32/bupropion SR 360 or naltrexone SR 48/bupropion SR 360; SD = standard deviation;
SE = standard error.
Notes: *Sub-study analysis set* includes all subjects who were randomized in the sub-study, had a baseline ABPM measurement, were administered at least one tablet of study treatment, and had at least one investigator contact/assessment after the start of study treatment.
Results to Week 24 are based on the last observation at or prior to Week 24 carried forward.
p-values are based on type III sums of squares from the ANCOVA model that included treatment and pooled study center as main effects, with the baseline blood pressure as a covariate.

Average Daytime and Night-time ABPM Systolic and Diastolic Blood Pressure

The secondary objectives are summarized below:

- In the NB32/48 group, the average daytime ABPM systolic and diastolic blood pressures LS mean changes from baseline to endpoint (Week 52) were 0.17 mm Hg and 1.16 mm Hg, respectively. In contrast, the placebo group demonstrated decreases in average daytime systolic and diastolic blood pressures of -3.09 mm Hg and -1.90 mm Hg, respectively. The treatment differences for systolic and diastolic blood pressures were 3.26 mm Hg (p=0.039) and 3.06 mm Hg (p=0.007), respectively.

- The LS mean change from baseline in average night-time systolic blood pressure was

-1.63 mm Hg for NB32/48 and -2.07 mm Hg for placebo. The treatment difference was 0.44 mm Hg (95% CI [-2.83, 3.72]; p=0.789). The LS mean change in average night time diastolic blood pressure for NB32/48 was -0.36 mm Hg and for placebo was -1.89 mm Hg and the treatment difference was 1.53 mm Hg (95% CI [-0.77, 3.82]; p=0.190).

- Comparison of average daytime and nighttime systolic and diastolic blood pressures showed that normal circadian rhythm was maintained for both the NB32/48 and placebo groups.

Table 47: Average Daytime and Night-time ABPM Systolic and Diastolic Blood Pressure (mm Hg) LS Mean Change and Descriptive Statistics from Baseline to Endpoint: ABPM Sub-study Analysis Set (Trial NB- 303 ABPM)

	Baseline		Endpoint		Change from Baseline				
	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum	Mean (SD)	Minimum, Maximum	LS Mean (SE)	Diff (95% CI)	p-value
Daytime Systolic blood pressure (mm Hg)									
Placebo (N=38)	126.4 (10.3)	105.3, 152.1	123.7 (10.9)	106.5, 147.6	-2.7 (8.3)	-21.3, 17.4	-3.1 (1.4)		
NB32/48 (N=79)	126.0 (9.1)	108.7, 147.0	126.2 (10.6)	97.8, 151.7	0.2 (7.7)	-20.8, 25.0	0.2 (0.9)	3.3 (0.2,6.4)	0.039
Daytime Diastolic blood pressure (mm Hg)									
Placebo (N=38)	77.7 (8.9)	58.9, 95.1	76.1 (7.7)	63.0, 90.0	-1.6 (5.4)	-14.0, 7.9	-1.9 (1.0)		
NB32/48 (N=79)	77.9 (7.4)	60.1, 92.3	79.1 (8.4)	52.3, 102.1	1.2 (5.9)	-16.5, 22.8	1.2 (0.7)	3.1 (0.8, 5.3)	0.007
Night-time Systolic blood pressure (mm Hg)									
Placebo (N=38)	114.3 (9.1)	97.9, 138.5	112.2 (10.4)	93.9, 132.9	-2.2 (7.5)	-25.1, 10.5	-2.1 (1.4)		
NB32/48 (N=79)	112.9 (10.6)	93.9, 149.4	111.4 (10.8)	88.7, 135.7	-1.5 (9.2)	-24.0, 23.7	-1.6 (1.0)	0.4 (-2.8, 3.7)	0.789
Night-time Diastolic blood pressure (mm Hg)									
Placebo (N=38)	65.9 (7.7)	52.0, 78.9	63.7 (8.2)	51.6, 79.0	-2.2 (4.7)	-12.0, 5.2	-1.9 (1.0)		
NB32/48 (N=79)	64.3 (8.0)	48.5, 86.0	64.1 (7.3)	49.2, 84.4	-0.1 (7.0)	-15.8, 17.1	-0.4 (0.7)	1.5 (-0.8, 3.8)	0.190

Source: Orexigen's Section 14, Table 14.3-10; Table 14.3-11; Table 14.3-14; Table 14.3-15
Abbreviations: CI = confidence interval; Diff = least squares mean difference; LS = least squares mean; mm Hg = millimeters of mercury; N = number of subjects per group;
NB32/48 = pooled group of subjects received either naltrexone SR 32/bupropion SR 360 or naltrexone SR 48/bupropion SR 360; SD = standard deviation; SE = standard error.
Notes: *Sub-study analysis set* includes all subjects who were randomized in the sub-study, had a baseline ABPM measurement, were administered at least one tablet of study treatment, and had at least one investigator contact/assessment after the start of study treatment.
Endpoint is the last available data while on study medication (last observation carried forward analyses). *p-values* are based on type III sums of squares from the ANCOVA model that included treatment and pooled study center as main effects, with the baseline blood pressure as a covariate.

An additional secondary objective of this sub-study was to evaluate the change from baseline in 24-hour blood pressure load (defined as percentage of readings with both systolic >135 mm Hg and diastolic >85 mm Hg over 24 hours). These measures were obtained at baseline (prior to administration of study drug), Week 24, and endpoint (Week 52). 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 LS mean change in the average 24-hour pulse rate was +0.05 bpm for NB32/48 and -0.52 bpm for placebo from baseline to endpoint. The treatment difference was 0.57 bpm (95% CI [-1.81, 2.94; p=0.635).

Orexigen's Proposed Label for Contrave regarding Blood Pressure Elevations
The proposed label includes the following guidance regarding blood pressure elevations:

- **2 DOSAGE AND ADMINISTRATION**
  Patients may experience elevated blood pressure during CONTRAVE treatment; the risk may be greater during the initial 3 months of therapy (Section 5.5, Hypertension). If clinically relevant elevations in blood pressure persist, discontinuation of CONTRAVE should be considered. As patients with hypertension may be at increased risk of blood pressure elevations, care should be exercised when initiating treatment with CONTRAVE in such patients.
- **5 WARNINGS AND PRECAUTIONS**
  5.5 Hypertension
  "In clinical practice with other bupropion containing products, hypertension, in some cases severe, requiring acute treatment, has been reported." This is followed by a description of changes in mean blood pressure, blood pressure adverse reactions, and vital sign outliers. The section concludes with the following precaution: "There is no clinical experience establishing the safety of CONTRAVE in patients with a recent history of myocardial infarction or unstable heart disease. Because CONTRAVE can increase blood pressure and/or pulse rate, care should be exercised when treating such patients."

6.3.4.2. Cardiovascular Events

As per the prescribing label for bupropion, there is no clinical experience establishing the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease. A review of the literature shows that the safety of bupropion used for smoking cessation was evaluated in hospitalized smokers with acute cardiovascular disease.[35] A five-hospital 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. The authors note that bupropion and placebo groups did not differ in cardiovascular mortality at 1 year (0% vs 2%), in blood pressure at follow-up, or in cardiovascular events at end-of- treatment (16% vs 14%, incidence rate ratio [IRR] 1.22 (95% CI: 0.64-2.33) or 1 year (26% vs 18%, IRR 1.56, 95% CI 0.91-2.69).

35 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.

However, while almost all of the safety outcome measures did not reach statistical significance, it is important to note that the incidence rate ratio for cardiovascular events at different time points all trend in the direction of harm for the drug. In addition, 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 provides limited insight into long-term use in a trial designed to assess CV outcomes.

Table 48: 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‡			
Intention to treat analysis			
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)
Analysis by study drug use§	*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 non-cardiovascular 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 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.

Another double-blind, multicenter trial randomized, in a 1:1 ratio, 629 subjects with stable CVD who smoked ≥10 cigarettes/day to receive bupropion SR (150 mg twice daily) or placebo for 7

weeks, with a follow-up of 52 weeks.[36] In both groups, there were no clinically significant changes in blood pressure and heart rate throughout the treatment phase. In total, 38 subjects (6%) reported cardiovascular adverse events (bupropion SR, n=24; placebo n=14). The most common were angina pectoris (bupropion SR n=7; placebo n=4), hypertension (bupropion SR n=2; placebo n=3, and palpitations (bupropion SR n=4; placebo n=1). Again, the short duration of bupropion use (7 weeks), limits the value of this trial to assess CV risk with chronic use.

The Cardiovascular special topic consisted of subtopics, categories, and preferred terms that are detailed in Appendix D1.

Overall, a greater percentage of subjects experienced Cardiovascular TEAEs in the Total NB group compared with the placebo group (8.1% and 7.6%, respectively) in the Primary Dataset.

Table 49: Incidence of Cardiovascular Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Cardiovascular Subtopic	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Double-Blind Treatment Phase				
Subjects with Any CV-Related TEAE	**115 (7.6%)**	**54 (8.5%)**	**205 (8.1%)**	**262 (8.1%)**
Subjects with any treatment-emergent SAE	**7 (0.5%)**	**1 (0.2%)**	**8 (0.3%)**	**9 (0.3%)**
Subjects discontinued due to AE	**21 (1.4%)**	**8 (1.3 %)**	**21 (0.8%)**	**30 (0.9%)**

Data Source: Applicant's Tables ISS.P.CV.1-1, ISS.P.CV.2-1, and ISS.P.CV.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Among the subjects who reported Cardiovascular special topic events, initial onset was observed in approximately 50% of subjects within the first 8 weeks in the Total NB group, compared to approximately 35% in the placebo group.

Table 50: Time-to-Onset and Duration of TEAEs-Cardiovascular: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)	Total NB (N=3239)
Time-to-onset of TEAEs CV-Related, n (%)	115 (7.6%)	262 (8.1%)
>0 to 4 weeks	21 (18.3%)	95 (36.3%)
>4 to 8 weeks	19 (16.5%)	40 (15.3%)
>8 to 12 weeks	10 (8.7%)	25 (9.5%)
>12 to 16 weeks	9 (7.8%)	18 (6.9%)
>16 to 20 weeks	8 (7.0%)	10 (3.8%)

36 Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J. 2003 May; 24(10):946-955.

	Placebo (N=1515)	Total NB (N=3239)
>20 to 24 weeks	7 (6.1%)	10 (3.8%)
>24 to 28 weeks	11 (9.6%)	14 (5.3%)
>28 to 32 weeks	4 (3.5%)	10 (3.8%)
>32 to 36 weeks	5 (4.3%)	5 (1.9%)
>36 to 40 weeks	6 (5.2%)	13 (5.0%)
>40 to 44 weeks	3 (2.6%)	4 (1.5%)
>44 to 48 weeks	4 (3.5%)	4 (1.5%)
>48 to 52 weeks	1 (0.9%)	4 (1.5%)
>52 to 56 weeks	4 (3.5%)	8 (3.1%)
>56 weeks	3 (2.6%)	2 (0.8%)
Mean (SD)	19.5 (16.2)	14.6 (15.3)
Median	16.0	7.5
Duration (weeks)		
Mean (SD)	10.22 (14.1)	8.24 (12.8)
Median	3.0	2.0

Atherosclerotic Disease
Major cardiovascular (CV) events were defined as cardiovascular death, myocardial infarction, and cerebrovascular accident. There was one death in the NB clinical program, attributed to myocardial infarction in a NB-treated subject. Two additional subjects, both in the NB32 group, experienced myocardial infarction and one placebo subject experienced cerebrovascular accident. An additional subject, in the NB16 group, experienced a post-treatment myocardial infarction 36 days after discontinuing study drug. Patient narratives can be found in Appendix C1 and C2.

Major CV (MACE): There were 4 major CV TEAEs reported during the clinical development program: 1 cerebrovascular accident (placebo group) and 3 myocardial infarctions (NB group). The events occurred on Days 56, 85, 90 and 324. The age range of subjects experiencing Major CV events was 44-65 years.

The CVA occurred in a placebo-treated subject with a history of hypertension. Of the 3 TEAEs of myocardial infarction observed among NB-treated subjects, 1 had no known prior CV events, 1 had a history of arrhythmia (idiopathic bradycardia), and 1 had a medical history of ischemia (active coronary artery disease, angina pectoris). The 1 myocardial infarction that occurred in a subject 36 days after last dose of study medication occurred in a subject previously treated with NB who had a history of hypertension.

Reviewer Comment: There were only 4 MACE events in the clinical trial database and the MACE events were not formally adjudicated. This reviewer is unable to adequately assess CV risk based on the data generated in this trial due to the small number of events and the baseline health of the trial population. Of the three myocardial infarctions in the clinical trial database, all occurred on NB. The label proposed by Orexigen does not exclude individuals at increased CV risk. There is a reference to individuals with a recent history of myocardial infarction or unstable heart disease in Warnings and Precautions, Section 5.5 Hypertension: "There is no

clinical experience establishing the safety of CONTRAVE in patients with a recent history of myocardial infarction or unstable heart disease. Because CONTRAVE can increase blood pressure and/or pulse rate, care should be exercised when treating such patients."

Table 51: Incidence of TEAEs-Atherosclerotic Disease: Primary Dataset, Double-Blind Treatment Phase

Cardiovascular Subtopic: Atherosclerotic Disease	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with Any Atherosclerotic-Related TEAE	**86 (5.7%)**	**42 (6.6%)**	**164 (6.4%)**	**208 (6.4%)**
Major CV	1 (<0.1%)	0	3 (0.1%)	3 (<0.1%)
Angina	4 (0.3%)	1 (0.2%)	7 (0.3%)	8 (0.2%)
Potential CV symptoms	63 (4.2%)	38 (6.0%)	107 (4.2%)	147 (4.5%)
ECG changes, other	20 (1.3%)	3 (0.5%)	50 (2.0%)	53 (1.6%)
Potential stroke symptoms	3 (0.2%)	1 (0.2%)	8 (0.3%)	9 (0.3%)
Subjects with any treatment-emergent SAE	**6 (0.4%)**	**1 (0.2%)**	**6 (0.2%)**	**7 (0.2%)**
Major CV	1 (<0.1%)	0	3 (0.1%)	3 (<0.1%)
Angina	3 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Potential CV symptoms	2 (0.1%)	1 (0.2%)	2 (<0.1%)	3 (<0.1%)
ECG changes, other	0	0	0	0
Potential stroke symptoms	0	0	0	0
Subjects discontinued due to AE	**13 (0.9%)**	**6 (0.9 %)**	**12 (0.5%)**	**19 (0.6%)**
Major CV	1 (<0.1%)	0	2 (<0.1%)	2 (<0.1%)
Angina	1 (<0.1%)	0	0	0
Potential CV symptoms	10 (0.7%)	6 (0.9 %)	8 (0.3%)	15 (0.5%)
ECG changes, other	1 (<0.1%)	0	2 (<0.1%)	2 (<0.1%)
Potential stroke symptoms	0	0	0	0

Data Source: Applicant's Tables ISS.P.CV.1-1, ISS.P.CV.2-1, and ISS.P.CV.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Angina: The Angina category included subjects with preferred terms of angina pectoris and coronary artery disease or occlusion as well as angiopathy and troponin increased. Of the 12 subjects with events in this category, three were not of atherosclerotic origin including two events of angiopathy (superficial vessels of the face or temporal artery) and an event of increased troponin association with superventricular tachycardia. Of the remaining nine subjects with angina or coronary events, three underwent coronary revascularization procedures (1 NB32: 2 Placebo).

Potential CV Symptoms: Potential CV Symptom events (defined by the sponsor as preferred terms of palpitations, chest pain, cardiac murmur, peripheral edema, etc) occurred at a similar incidence in the Total NB and placebo groups (4.5% and 4.2%, respectively). No subject experiencing Potential CV symptoms also experienced a Major CV event. Potential CV symptom events were serious in 3 of 147 Total NB subjects and in 2 of 63 placebo subjects and led to treatment discontinuation in 0.5% Total NB vs. 0.7% placebo.

Arrhythmias

Arrhythmias occurred in 1.5% of subjects in the Total NB group and 1.8% of placebo subjects. No Arrhythmia events were serious in the Total NB group vs. three in the placebo group and these events rarely led to discontinuation of study drug. Events reported by ≥0.1% subjects included tachycardia (0.6% Total NB vs. 0.1% placebo), electrocardiogram QT prolonged (8, 0.2% Total NB vs. 4, 0.3% placebo), atrial fibrillation (<0.1% Total NB vs. 0.3% placebo), first degree atrioventricular block (<0.1% Total NB vs. 0.3% placebo), atrioventricular block (<0.1% Total NB vs. 0.1% placebo), and arrhythmia (<0.1% Total NB vs. 0.2% placebo).

Table 52: Incidence of TEAEs-Arrhythmias: Primary Dataset, Double-Blind Treatment Phase

Arrhythmias Subtopic	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with Any Arrhythmia TEAE	**27 (1.8%)**	**12 (1.9%)**	**35 (1.4%)**	**47 (1.5%)**
Arrhythmias, atrial	8 (0.5%)	4 (0.6%)	6 (0.2%)	10 (0.3%)
Arrhythmias, other	6 (0.4%)	4 (0.6%)	21 (0.8%)	25 (0.8%)
Repolarization abnormalities	4 (0.3%)	3 (0.5%)	5 (0.2%)	8 (0.2%)
Conduction disorders	10 (0.7%)	1 (0.2%)	5 (0.2%)	6 (0.2%)
Subjects with any treatment-emergent Arrhythmia SAE	**3 (0.2%)**	**0**	**0**	**0**
Arrhythmias, atrial	2 (0.1%)	0	0	0
Arrhythmias, other	1 (<0.1%)	0	0	0
Repolarization abnormalities	0	0	0	0
Conduction disorders	0	0	0	0
Subjects discontinued due to Arrhythmia AE	**7 (0.5%)**	**1 (0.2%)**	**4 (0.2%)**	**5 (0.2%)**
Arrhythmias, atrial	4 (0.3%)	0	1 (<0.1%)	1 (<0.1%)
Arrhythmias, other	0	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Repolarization abnormalities	2 (0.1%)	0	2 (<0.1%)	2 (<0.1%)
Conduction disorders	1 (<0.1%)	0	0	0

Data Source: Applicant's Tables ISS.P.CV.1-1, ISS.P.CV.2-1, ISS.P.CV.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Congestive Heart Failure

Congestive heart failure incidence was 0.7% in the Total NB and 0.9% in the Placebo group and <0.1% subjects reported an SAE of congestive heart failure in both the Total NB and placebo groups. No subject experiencing congestive heart failure or potential congestive heart failure (defined by the sponsor as preferred terms of cardiomegaly, dyspnea, pulmonary congestion, etc) experienced a Major CV event or underwent a revascularization procedure. Discontinuations due to Congestive Heart Failure or Potential CHF Symptoms were one subject (<0.1%) in the placebo group with pericardial effusion, and 6 subjects (0.2%) in the Total NB group (1 with congestive heart failure, and 5 with dyspnea or dyspnea exertional).

Table 53: Incidence of TEAEs-Congestive Heart Failure: Primary Dataset, Double-Blind Treatment Phase

CHF Subtopic	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with Any CHF TEAE	**13 (0.9%)**	**4 (0.6%)**	**19 (0.7%)**	**24 (0.7%)**
Congestive heart failure	0	0	2 (<0.1%)	2 (<0.1%)
Potential CHF Symptoms	13 (0.9%)	4 (0.6%)	17 (0.7%)	22 (0.7%)
Subjects with any treatment-emergent CHF SAE	**1(<0.1%)**	**0**	**3 (0.1%)**	**3 (<0.1%)**
Congestive heart failure	0	0	1 (<0.1%)	1 (<0.1%)
Potential CHF Symptoms	1(<0.1%)	0	2 (<0.1%)	2 (<0.1%)
Subjects discontinued due to CHF AE	**1(<0.1%)**	**1 (0.2%)**	**5 (0.2%)**	**6 (0.2%)**
Congestive heart failure	0	0	1 (<0.1%)	1 (<0.1%)
Potential CHF Symptoms	1(<0.1%)	1 (0.2%)	4 (0.2%)	5 (0.2%)

Data Source: Applicant's Tables ISS.P.CV.1-1, ISS.P.CV.2-1, ISS.P.CV.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

6.3.4.3 Seizure and Convulsions

According to the prescribing information for bupropion, the seizure rate associated with doses of sustained-release bupropion up to 300 mg/day is approximately 0.1% (1/1,000). Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (4/1,000) in depressed patients treated at doses in a range of 300 to 450 mg/day. Because the use of bupropion is associated with a dose-dependent risk of seizures, clinicians are advised not to prescribe doses over 300 mg/day for smoking cessation. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose. The risk of seizure is also related to patient factors, clinical situations, and concomitant medications.

Within the NB clinical development program, the only preferred terms related to the Seizure and Convulsions special topic were convulsion and grand mal convulsion. Two subjects (2/3239, 0.06%) in the NB32 group, compared to none in the placebo group, experienced an isolated seizure. Both subjects had no prior seizure history. Narratives for these subjects are in Appendix C3.

6.3.4.4. Suicide-related Events

A retrospective assessment tool of suicidality, the Columbia Classification Algorithm of Suicide Assessment (C-CASA)[37] was used to assess AEs that could represent suicidal events (behavior and ideation) during Phase 2b and 3trials. The results of the C-CASA analyses for the

37 Columbia Classification Algorithm of Suicide Assessment (C-CASA): A method of retrospectively analyzing a clinical trial database for cases of suicide. See Posner K, et al. Columbia Classification. Algorithm of Suicide

five placebo-controlled clinical trials (NB-201, NB-301, NB-302, NB-303, and NB-304) were pooled. The classification of Possibly Suicide-Related Adverse Events (PSRAEs) was based upon C-CASA categorization as follows:

- No event (Code 0)
- Completed suicide (Code 1)
- Suicide attempt (Code 2)
- Preparatory acts towards eminent suicide behavior (Code 3)
- Suicidal ideation (Code 4)
- Self-injurious behavior, intent unknown (Code 5)
- Not enough information [Fatal] (Code 6)
- Other [No evidence of suicidality or deliberate self-harm] (Code 8)
- Not enough information [Non-fatal] (Code 9)

The primary endpoint of this pooled analysis was suicidal ideation or worse (Codes 1, 2, 3, or 4 combined), also called suicidality or suicidal behavior and ideation, based upon the C-CASA categorization. There were no completed suicides, suicide attempts, or preparatory acts toward imminent suicidal behavior in any treatment group. There were four events of suicidal ideation or behavior during this trial, one event (1/3239, <0.1%) in the Total NB treatment group (Subject 020-NB-303-016) compared to three events (3/1515, 0.2%) in the placebo treatment group (Subjects 32-NB-302-059, 36-NB-302-113, and 061-NB-304-010).

Table 54: Incidence Rates for Suicidality by Outcome Codes by Trial and Overall (Safety Analysis Population)

	By Trial					By Treatment	
C-CASA Classification, n(%)	**NB-201 (N=273)**	**NB-301 (N=1711)**	**NB-302 (N=784)**	**NB-303 (N=1484)**	**NB-304 (N=502)**	**Total NB (N=3239)**	**Placebo (N=1515)**
No Event (Code 0)*	267 (97.8)	1633 (95.4)	734 (93.6)	1418 (95.6)	467 (93.0)	3075 (94.9)	1444 (95.3)
Completed Suicide (Code 1)	0	0	0	0	0	0	0
Suicide Attempt (Code 2)	0	0	0	0	0	0	0
Preparatory Acts Toward Imminent Suicidal Behavior (Code 3)	0	0	0	0	0	0	0
Suicidal Ideation (Code 4)	0	0	2 (0.3)	1 (< 0.1)	1 (0.2)	1 (<0.1)	3 (0.2)
Self-Injurious Behavior, Intent Unknown (Code 5)	0	0	0	0	0	0	0
Not Enough Information, Fatal (Code 6)	0	0	0	0	0	0	0
Other, No evidence of suicidality or deliberate self-harm (Code 8)	6 (2.2)	77 (4.5)	48 (6.1)	65 (4.4)	34 (6.8)	162 (5.0)	68 (4.5)
Not Enough Information, Non-Fatal (Code 9)	0	1 (< 0.1)	0	0	0	1 (<0.1)	0

Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007 Jul; 164(7):1035-43.

	By Trial					By Treatment	
C-CASA Classification, n(%)	**NB-201 (N=273)**	**NB-301 (N=1711)**	**NB-302 (N=784)**	**NB-303 (N=1484)**	**NB-304 (N=502)**	**Total NB (N=3239)**	**Placebo (N=1515)**
Suicidal Ideation or Worse (Codes 1, 2, 3, 4)	0	0	2 (0.3)	1 (< 0.1)	1 (0.2)	1 (<0.1)	3 (0.2)
Suicidal Preparatory Actions or Worse (Codes 1, 2, 3)	0	0	0	0	0	0	0

The safety analysis set includes all randomized subjects who were administered at least one tablet of study drug treatment and had at least one investigator contact/assessment at any time after start of study treatment.
Individual study columns include all subjects who received NB or placebo. The Total NB and Placebo columns include only subjects who received NB or placebo, respectively.
*No event is defined as absence of PSRAE.

A secondary objective of the suicidality meta-analysis was to assess change from baseline in IDS-SR item 18 scores (which specifically address suicidality). The Overall odds ratio comparing placebo to Total NB calculated for changes in IDS-SR item 18 scores from 0 or 1, to 2 or 3, were 0.92 (95% CI: 0.44, 2.04).

This pooled suicidality analysis suggests that, in these trials, NB is not associated with increased suicidal ideation or behavior. Of note, the NB database is relatively small (NB: 3200; Placebo: 1500) as compared to other databases such as Rimonabant, with a database of ~13,000, where increased suicidality was demonstrated.

6.3.4.5. Psychiatric Events

The Psychiatric special topic consisted of subtopics, categories, and preferred terms that are detailed in Appendix D2.

There were a higher percentage of subjects with Psychiatric events in the Total NB group compared with the placebo group (20.8% and 15.5%, respectively) in the Primary Dataset. The top three subtopics were the Sleep Disorders subtopic (12.8% Total NB and 8.4% placebo), the Depression subtopic (6.0% Total NB and 5.9% placebo), and the Anxiety subtopic (5.7% Total NB and 4.4% placebo).

Serious Psychiatric events were rare (reported in one subject [anxiety in NB32 Subject 019-NB-303-001]) and discontinuations due to Psychiatric events were reported in a similar percentage of subjects in the Total NB and placebo groups (3.3% and 3.0%, respectively).

Subjects with a prior history of depression experienced higher rates of Psychiatric events than subjects without a history of depression in both Total NB (30.9% vs. 19.6%) and placebo (25.9% vs. 14.0%) groups, respectively. A history of anxiety was also associated with a higher incidence of psychiatric events in both Total NB (31.0% vs. 20.4%) and placebo (27.0% vs. 15.0%) groups.

Subjects ≥65 years of age in the Total NB group experienced more Psychiatric Disorders SOC events (27.4%) compared to placebo (6.3%) although the sample size was small (62, 32) for

Total NB and placebo, respectively. The majority of events were due to insomnia (11.3% Total NB, 3.1% placebo) and depression (6.5% Total NB, 3.1% placebo).

Table 55: Incidence of Psychiatric Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Psychiatric TEAEs	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with Any TEAE	**235 (15.5%)**	**102 (16.1%)**	**565 (22.2%)**	**674 (20.8%)**
Anxiety	66 (4.4%)	26 (4.1%)	155 (6.1%)	186 (5.7%)
Depression	90 (5.9%)	30 (4.7%)	161 (6.3%)	194 (6.0%)
Sleep Disorders	128 (8.4%)	63 (10.0%)	350 (13.8%)	416 (12.8%)
Hostility	33 (2.2%)	8 (1.3%)	84 (3.3%)	94 (2.9%)
Mood disorders	11 (0.7%)	3 (0.5%)	30 (1.2%)	33 (1.0%)
Psychosis	1 (<0.1%)	0	26 (1.0%)	26 (0.8%)
Non-specific mental disorders	4 (0.3%)	1 (0.2%)	12 (0.5%)	13 (0.4%)
Subjects with any treatment-emergent SAE	**0**	**0**	**1(<0.1%)**	**1(<0.1%)**
Anxiety	0	0	1(<0.1%)	1(<0.1%)
Subjects discontinued due to AE	**46(3.0%)**	**17 (2.7%)**	**85 (3.3%)**	**106 (3.3%)**
Anxiety	13 (0.9%)	1 (0.2%)	24 (0.9%)	27 (0.8%)
Depression	25 (1.7%)	9 (1.4%)	22 (0.9%)	33 (1.0%)
Sleep Disorders	9 (0.6%)	7 (1.1%)	26 (1.0%)	34 (1.0%)
Hostility	3 (0.2%)	1 (0.2%)	11 (0.4%)	14 (0.4%)
Mood disorders	1 (<0.1%)	1 (0.2%)	5 (0.2%)	6 (0.2%)
Psychosis	0	0	7 (0.3%)	7 (0.2%)
Non-specific mental disorders	1 (<0.1%)	0	0	0

Data Source: Applicant's Tables ISS.P.PSY.1-1, ISS.P.PSY.2-1, and ISS.P.PSY.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Among the subjects who reported Psychiatric events, initial onset was observed in approximately 65% of subjects within the first 4 weeks in the Total NB group, compared to approximately 43% in the placebo group. Looking at the first 8 weeks, initial onset was observed in 77% in the Total NB group compared to 58% in the placebo group.

Median time to onset was 3 weeks for Total NB compared to 6 weeks for placebo. A similar median duration of 4 weeks and 5 weeks was observed for Psychiatric events in the Total NB and placebo groups, respectively.

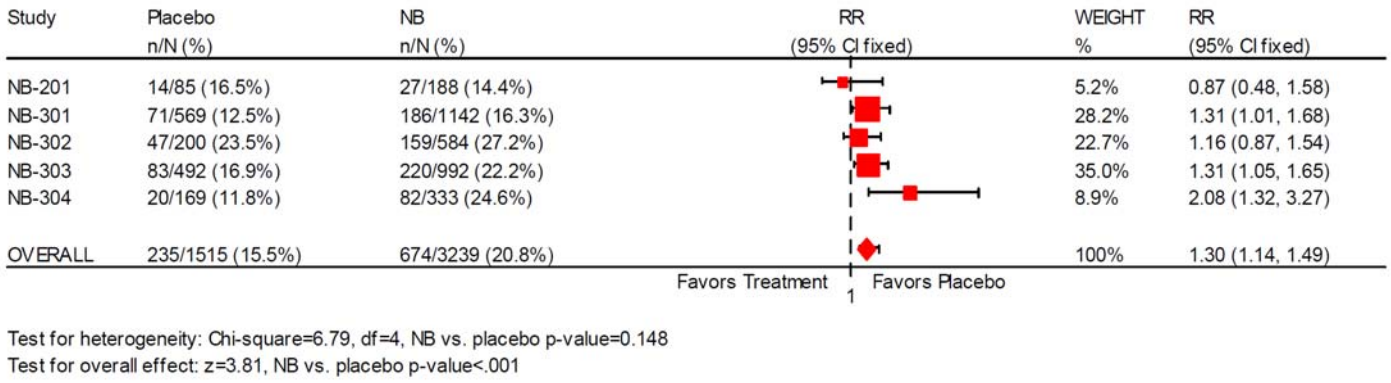
Table 56: Time-to-Onset and Duration of TEAEs-Psychiatric: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)	Total NB (N=3239)
Time-to-onset of TEAEs Psychiatric-Related, n (%)	235 (15.5%)	674 (20.8%)
>0 to 4 weeks	100 (42.6%)	436 (64.7%)
>4 to 8 weeks	35 (14.9%)	81 (12.0%)

	Placebo (N=1515)	Total NB (N=3239)
>8 to 12 weeks	20 (8.5%)	37 (5.5%)
>12 to 16 weeks	17 (7.2%)	28 (4.2%)
>16 to 20 weeks	11 (4.7%)	12 (1.8%)
>20 to 24 weeks	7 (3.0%)	16 (2.4%)
>24 to 28 weeks	10 (4.3%)	11 (1.6%)
>28 to 32 weeks	6 (2.6%)	9 (1.3%)
>32 to 36 weeks	8 (3.4%)	13 (1.9%)
>36 to 40 weeks	6 (2.6%)	9 (1.3%)
>40 to 44 weeks	4 (1.7%)	7 (1.0%)
>44 to 48 weeks	3 (1.3%)	5 (0.7%)
>48 to 52 weeks	4 (1.7%)	4 (0.6%)
>52 to 56 weeks	4 (1.7%)	4 (0.6%)
>56 weeks	0	2 (0.3%)
Mean (SD)	12.5 (13.9)	7.6 (11.2)
Median	6	3
Duration (weeks)		
Mean (SD)	11.0 (13.3)	11.2 (15.5)
Median	5	4

The overall relative risk of the combined Psychiatric events was increased (RR = 1.30; 95% CI = 1.14 - 1.49) in NB treated subjects compared to placebo.

Figure 13: Relative Risk of Treatment-Emergent Adverse Events Psychiatric Adverse Events Safety Analysis Set, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset



Data Source: Orexigen's Figure ISS.P.PSY.1-2

Anxiety

The AE incidence in the Anxiety subtopic was greater in the Total NB group compared to placebo [186, (5.7%) and 66, (4.4%), respectively]. Most NB-treated subjects with Anxiety events had an onset during the first 4 weeks of treatment (53.8% Total NB vs. 18.2% placebo). The median time to onset was 4 weeks in the Total NB group and 14 weeks in the placebo group. The median duration was 3 weeks in the Total NB groups and 5 weeks in the placebo groups.

Serious Anxiety events were rare (reported in one subject [anxiety in NB32 Subject 019-NB-303-001]) and discontinuations due to Anxiety events were reported in a similar percentage of subjects in the Total NB and placebo groups (0.8% and 0.9%, respectively).

Subjects with a history of anxiety had a higher incidence of Anxiety events than subjects without a history of anxiety (12.7% vs. 5.5%) for Total NB and (15.9% vs. 3.9%) for placebo, respectively. Subjects with a history of depression also had a higher incidence of Anxiety events than subjects without a history of depression: 11.0% vs. 5.1% for Total NB and 7.8% vs. 3.9% for placebo, respectively.

Depression
The AE incidence in the Depression subtopic was similar between treatment groups (6.0% Total NB and 5.9% placebo). Depression events that were severe occurred in 0.4% [12/3239] of Total NB and 0.3% [5/1515] of placebo.

Sixty-three percent of NB-treated subjects with Depression events had an onset during the first 8 weeks of treatment compared to 49% of Placebo-treated subjects. The median time to onset was 4 weeks in the Total NB group and 9 weeks in the placebo group. The median duration[38] was similar: 4 weeks and 5 weeks in the Total NB and placebo groups, respectively.

Discontinuations due to AEs were lower in the Total NB group (1.0%) compared to placebo (1.7%). Subjects with a history of depression had a higher incidence of Depression events than subjects without a history of depression: 8.8% vs. 5.6% for Total NB and 16.1% vs. 4.5% for placebo, respectively.

Sleep Disorders
The Sleep Disorders subtopic included events related to sleep disturbances as well as somnolence and sedation. The AE incidence in the Sleep Disorders subtopic was higher in the Total NB group compared with placebo (12.8% Total NB and 8.4% placebo). Among the subjects who reported a sleep disorder TEAE, initial onset was observed in 81% of subjects within the first 8 weeks in the Total NB group, compared to 68% in the placebo group and a similar median duration of 5 weeks and 6 weeks in the Total NB and placebo groups, respectively.

Insomnia was the most frequently occurring TEAE (8.6% Total NB and 5.9% placebo) in the Sleep Disorders category. Of the subjects who reported Insomnia, the use of sedatives and hypnotics on or after the start of study drug was 17.3% for Total NB and 20.5% for the placebo group. Insomnia was more frequent in subjects with a history of anxiety compared to those without in both Total NB (11.9% vs. 8.4%) and placebo subjects (9.5% vs. 5.7%). A history of depression was also associated with a higher incidence of insomnia in the Total NB group (13.9% vs. 7.9%) and in the placebo group (7.8% vs. 5.6%). No SAEs were reported in this subtopic and discontinuations due to AEs were slightly higher in the Total NB group (1.0%) as compared to the placebo group (0.6%).

38 The duration of the specified AE (i.e., only those events that are presented in the time to AEs) is defined as the difference between the stop date and the start date of the AE + 1 day

Hostility, Mood Disorders, Psychosis, and Non-specific Mental Disorders

- The AE incidence in the Hostility subtopic was slightly higher in the Total NB group compared with placebo (2.9% Total NB and 2.2% placebo).
- The AE incidence in the Mood disorders subtopic was slightly higher in the Total NB group compared with placebo (1.0% Total NB and 0.7% placebo).
- The AE incidence in the non-specific mental disorders subtopic was similar for the Total NB group and the placebo group (0.4% Total NB and 0.3% placebo).
- However, the AE incidence in the Psychosis disorders subtopic was higher in the Total NB group compared with placebo (0.8% Total NB and <0.1% placebo).

The placebo group had only one report of potential psychosis (depersonalization) and no reports of psychosis events. Of the Total NB subjects with events in the Psychosis subtopic, 18/26 reported either dissociation (10) or agitation (8). The verbatim terms for the dissociation preferred term were spaciness, or feeling detached or disconnected. One severe event of agitation occurred in an NB32 subject. The other reports of potential psychosis were one report each of depersonalization, flat affect, hypervigilence, suspiciousness, and thinking abnormal. There were 3 psychosis reports (as opposed to potential psychosis) and all 3 occurred in the NB group: 2 reports of hallucination and one report of paranoia.

Discontinuations in the NB group in this subtopic were due to dissociation (4), agitation (2) and hallucination (1); no placebo subjects in this subtopic discontinued.

IDS-SR Scores

During the Phase 3 trials, changes in mood or depressive symptoms were routinely monitored using the self-administered 30-item IDS-SR questionnaire[39]. The IDS-SR is scored from 0-84 with a score of 0-13 indicative of no depression, 14-25 mild, 26-38 moderate, 39-48 severe, and ≥49 very severe[40]. At baseline subjects were required to have an IDS-SR total score <30 and scores <2 on items 5 (sadness), 6 (irritability), 7 (anxiety/tension) and 18 (suicidality). The LS mean Total IDS-SR scores at baseline were 6.82 and 6.62 for Total NB and placebo subjects, respectively. Thus, baseline IDS-SR scores in all trials were low and in the normal range, indicating that the subjects participating in the Phase 3 trials had minimal or no depressive symptomatology. The change from baseline was slightly higher for the Total NB group compared with placebo (0.29 Total NB and -0.41 placebo).

6.3.4.6. Cognitive Disorders

The Cognitive Disorders special topic consisting of subtopics, categories, and preferred terms is detailed in Appendix D3.

The Cognitive Disorders topic includes two separate subtopics: the Cognitive subtopic reflects changes in mental functioning as well as sleepiness, and the Dizziness and Syncope subtopic

39 Rush AJ, Gullion CM, Basco MR, Jarrett RB, and Trivedi MH. The inventory of depressive symptomatology (IDS): Psychometric properties. Psychological Medicine. 1996;26:477-486.
40 www.ids-qids.org

includes two categories: dizziness or lightheadedness, and changes in level of consciousness such as syncope.

There was a greater incidence of the combined Cognitive Disorders events in the Total NB group compared with the placebo group (14.2% and 5.5%, respectively) in the Primary Dataset. The greatest incidence of events was in the Dizziness category where 10.0% of Total NB and 3.4% of placebo subjects experienced events. SAEs occurred in <0.1% in both groups and 2.5% of Total NB group versus 0.7% of placebo subjects discontinued for a Cognitive Disorders event.

Table 57: Incidence of Cognitive Disorders Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Cognitive TEAEs	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with Any TEAE	**83 (5.5%)**	**72 (11.4%)**	**381 (15.0%)**	**461 (14.2%)**
Cognitive Disorders	31 (2.0%)	26 (4.1%)	138 (5.4%)	166 (5.1%)
Attention Disorders	9 (0.6%)	11 (1.7%)	63 (2.5%)	74 (2.3%)
Thinking Disorders	7 (0.5%)	2 (0.3%)	30 (1.2%)	32 (1.0%)
Memory Disorders	5 (0.3%)	3 (0.5%)	20 (0.8%)	24 (0.7%)
Somnolence	12 (0.8%)	11 (1.7%)	33 (1.3%)	45 (1.4%)
Dizziness and Syncope	55 (3.6%)	54 (8.5%)	269 (10.6%)	330 (10.2%)
Dizziness	51 (3.4%)	52 (8.2%)	264 (10.4%)	323 (10.0%)
Syncope	5 (0.3%)	2 (0.3%)	12 (0.5%)	14 (0.4%)
Subjects with any treatment-emergent SAE	**1 (<0.1%)**	**0**	**2(<0.1%)**	**2(<0.1%)**
Dizziness	1 (<0.1%)	0	0	0
Syncope	0	0	2 (<0.1%)	2 (<0.1%)
Subjects discontinued due to AE	**11(0.7%)**	**19 (3.0%)**	**58 (2.3%)**	**81 (2.5%)**
Cognitive Disorders	6 (0.4%)	5 (0.8%)	32 (1.3%)	37 (1.1%)
Attention Disorders	3 (0.2%)	2 (0.3%)	13 (0.5%)	15 (0.5%)
Thinking Disorders	3 (0.2%)	0	11 (0.4%)	11 (0.3%)
Memory Disorders	0	1 (0.2%)	2 (<0.1%)	3 (<0.1%)
Somnolence	0	2 (0.3%)	6 (0.2%)	8 (0.2%)
Dizziness and Syncope	5 (0.3%)	16 (2.5%)	26 (1.0%)	46 (1.4%)
Dizziness	5 (0.3%)	15 (2.4%)	24 (0.9%)	43 (1.3%)
Syncope	0	1 (0.2%)	2 (<0.1%)	3 (<0.1%)

Data Source: Applicant's Tables ISS.P.COG.1-1, ISS.P.COG.2-1, and ISS.P.COG.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Cognitive

There was a greater incidence of Cognitive subtopic events in the Total NB group compared to the placebo group (5.1% vs. 2.0%). None of the events were SAEs and 1.1% of Total NB group versus 0.4% of placebo subjects discontinued for a Cognitive event. The most common Cognitive events category was Attention Disorders (2.3% Total NB vs 0.6% placebo). Severe events were uncommon and occurred with similar frequency between the groups (4.2% NB vs 3.2% placebo). A medical history of depression was slightly more frequent in subjects experiencing Cognitive events than in the enrolled population in both Total NB and placebo

(approximately 16% with Cognitive events vs. 12% in the enrolled population). The percentage of subjects who experienced a cognitive disorder and then discontinued the trial due to the cognitive AEs was similar between the groups (22% NB vs 19% placebo).

Dizziness and Syncope
Events in the Dizziness/Syncope subtopic were common in Total NB (10.2%) and 2.8 times more frequent than in placebo (3.6%). The single preferred term dizziness accounted for almost all reported events (10% Total NB and 3.4% placebo). Two SAEs of syncope were reported in the NB32 group, and one SAE of dizziness was reported in the placebo group. Dizziness was the primary reason for discontinuation in 1.3% of Total NB and 0.3% of placebo subjects, while syncope rarely led to discontinuation (<0.1% of Total NB, 0 placebo).

Syncope (including altered state of consciousness and loss of consciousness) was infrequent and occurred at a similar incidence across groups (0.4% Total NB and 0.3% placebo). Two subjects in the Total NB group reported an SAE of syncope compared to zero in placebo and three NB subjects discontinued due to syncope compared to zero in placebo. Dizziness was not a precursor to syncope in most subjects; only one subject (119-NB-303-017) experienced dizziness within 30 days of an event of syncope. Hypotension and low blood pressure were rare events in the NB clinical trial program and not correlated with the occurrence of either dizziness or syncope. With the exception of one subject, descriptions of syncopal episodes were not consistent with seizure activity. Subject 066-NB-303-016, who experienced a temporal lobe seizure on Day 144, reported unobserved pre-syncope and syncope on Days 148 and 150, respectively. Some of the narratives from subjects that experienced syncope are provided in Appendix C4.

6.3.4.7. Renal Function

Increases in mean creatinine values from baseline to endpoint were seen in the clinical trial database for NB. In the Primary Dataset, larger mean changes in creatinine from baseline to endpoint were observed in the Total NB group compared with the placebo group (0.07 mg/dL NB vs 0.01 mg/dL PBO) and from baseline to maximum (0.15 mg/dL NB vs 0.07 mg/dL PBO).

Shifts to high creatinine at any postbaseline assessment occurred in a higher percentage of subjects in the Total NB group (7.6%) compared with the placebo group (1.9%). In the analysis of the diabetic subjects, a higher percentage of NB subjects experienced shifts to high creatinine as compared to placebo subjects (12.7% NB vs 3.1% PBO). Likewise, in the analysis of the non-diabetic subjects, a higher percentage of NB subjects experienced shifts to high creatinine as compared to placebo subjects (7.0% NB vs 1.7% PBO). Thus, subjects on NB-treatment were 4 times more likely to have a shift to high creatinine during the trial.

Subjects in both treatment groups generally had normal creatinine at baseline; 1.1% of placebo and 0.8% of Total NB subjects had a creatinine ≥ULN (1.20 mg/dL for females and 1.30 mg/dL for males). Mean creatinine values for Total NB subjects who subsequently had a value above the upper limit of normal were highest at Week 4 and declined somewhat thereafter.

Two (<0.1%) of 2769 subjects in the Total NB group and 0 of 1399 subjects in the placebo group each had a single creatinine measurement ≥2.0 mg/dL. Both returned to normal while continuing study drug.

For BUN, mean changes from baseline to endpoint and from baseline to maximum were lower in the Total NB group (0.02 and 1.75 mg/dL, respectively) compared with the placebo group (0.08 and 1.95 mg/dL, respectively), and shifts to high BUN and PCS values (≥30 mg/dL) at any postbaseline assessment were slightly less frequent in the Total NB group (2.5% and 0.3%, respectively) compared with the placebo group (3.4% and 0.6%, respectively).

The Renal Disorders subtopics and preferred terms are listed in Appendix D4.

Overall there was a slightly greater percentage of subjects with Renal Disorders in the Total NB group compared with the placebo group (4.8% and 3.8%, respectively) in the Primary Dataset. Renal Disorders SAEs and discontinuations were infrequent (≤0.1% Total NB and placebo). There were three discontinuations due to elevated creatinine (two in the NB32 group, one in the placebo group). All three subjects had normal creatinine at baseline and the elevations returned to normal after stopping study drug.

Table 58: Incidence of Renal Disorders Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Renal TEAEs	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Subjects with Any TEAE	**58 (3.8%)**	**156 (4.8%)**
Kidney Function†	8 (0.5%)	35 (1.1%)
Nephrolithiasis	6 (0.4%)	11 (0.3%)
Abnormal Urinalysis	4 (0.3%)	4 (0.1%)
Urinary infections	43 (2.8%)	110 (3.4%)
Lesions	0	1 (<0.1%)
Subjects with any treatment-emergent SAE	**1 (<0.1%)**	**4 (0.1%)**
Kidney Function†	0	0
Nephrolithiasis	1 (<0.1%)	3 (<0.1%)
Abnormal Urinalysis	0	0
Urinary infections	0	1 (<0.1%)
Lesions	0	0
Subjects discontinued due to AE	**1 (<0.1%)**	**4 (0.1%)**
Kidney Function†	1 (<0.1%)	2 (<0.1%)
Nephrolithiasis	0	0
Abnormal Urinalysis	0	0
Urinary infections	0	1 (<0.1%)
Lesions	0	1 (<0.1%)

Data Source: Applicant's Tables ISS.P.REN.1-1, ISS.P.REN.2-1, and Table ISS.P.REN.3-1.
†a collection of preferred terms such as creatinine increased, creatinine abnormal, BUN increased, urine output decreased, renal function test abnormal, etc
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug

discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event;
Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

This reviewer did additional analyses which confirmed a slightly greater percentage of subjects with Renal Events in the Total NB group compared with the placebo group in the Primary Dataset. The difference in incidence was primarily due to the preferred term blood creatinine increased. Overall, there were few subjects in either group with renal adverse events.

6.3.4.8. Liver and Gallbladder

The Liver and Gallbladder subtopics, categories, and preferred terms are listed in Appendix D5.

The incidence of Liver and Gallbladder special topic events was similar in the Total NB and placebo groups (1.9% and 1.7%, respectively) in the Primary Dataset and the incidence of SAEs (0.3% Total NB vs. <0.1% placebo subjects) and discontinuations (0.3% Total NB vs. 0.2% placebo subjects) were low.

Table 59: Incidence of Liver and Gallbladder-Related Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Hepatobiliary TEAEs	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Subjects with Any TEAE	**25 (1.7%)**	**62 (1.9%)**
Potential Hepatotoxicity	16 (1.1%)	38 (1.2%)
Gallbladder (cholelithiasis, cholecystitis)	7 (0.5%)	22 (0.7%)
Liver lesions	2 (0.1%)	4 (0.1%)
Subjects with any treatment-emergent SAE	**1 (<0.1%)**	**10 (0.3%)**
Potential Hepatotoxicity	0	1 (<0.1%)
Gallbladder (cholelithiasis, cholecystitis)	1 (<0.1%)	10 (0.3%)
Liver lesions	0	0
Subjects discontinued due to AE	**3 (0.2%)**	**10 (0.3%)**
Potential Hepatotoxicity	2 (0.1%)	8 (0.2%)
Gallbladder (cholelithiasis, cholecystitis)	1 (<0.1%)	2 (<0.1%)
Liver lesions	0	0

Data Source: Applicant's Tables ISS.P.LVR.1-1, ISS.P.LVR.2-1, and ISS.P.LVR.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event;
Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Two subjects discontinued due to Bilirubin events (placebo Subject 108-NB-304-005 and NB16 Subject 078-NB-301-071).

- NB16 Subject 078-NB-301-071 had an elevated baseline bilirubin of 1.5 mg/dL and a maximum value of 2.0 mg/dL (normal range 0.2-1.2 mg/dL) and indirect bilirubin of 1.2 mg/dL (normal range 0.1-1.0 mg/dL). Maximum bilirubin elevations did not exceed 2.1 mg/dL. ALT and AST

values remained within the normal range and bilirubin values returned to normal following study drug discontinuation.

- One subject (NB32 subject 24-NB-301-022) had an SAE of cholestatic hepatitis and chronic cholecystitis. Values for ALT, AST, and bilirubin returned to near normal 9 days after laparoscopic cholecystectomy.

Maximum Transaminase Elevations (Normal range for ALT is 6-48 IU/L for males and 6-37 IU/L for females; normal range for AST is 10-45 IU/L for males and 10-36 IU/L for females):

- NB32 Subjects: The maximum postbaseline value was 308 IU/L for ALT and 170 IU/L for AST (in Subject 087-NB-301-083), which decreased to 42 IU/L and 25 IU/L, respectively, 31 days after last dose.
- NB16 Subjects: The maximum postbaseline value was 621 IU/L for ALT and 311 IU/L for AST which decreased to 135 IU/L and 59 IU/L, respectively, 15 days after the last dose (095-NB-301-005).
- Placebo Subjects: The maximum postbaseline value was ALT and AST of 149 and 75 IU/L, respectively (103-NB-303-009).

Potentially Clinically Significant (PCS) Laboratory Values
For liver enzyme tests, no subjects had PCS values for total bilirubin or albumin. PCS values of >3x ULN were seen in ALT (0.3% of subjects in the Total NB group and 0.2% of subjects in the placebo group), and AST (0.1% of subjects in the Total NB group and 0.1% of subjects in the placebo group). No subjects met criteria for Hy's law classification[41].

Table 60: Potentially Clinically Significant Laboratory Values – Chemistry: Primary Dataset, Double-Blind Treatment Phase

	Placebo N=1515	NB16 N=633	NB32 N=2545	Total N=3239
ALT > 3x ULN	3/1229 (0.2%)	0/474	7/1919 (0.4%)	7/2430 (0.3%)
ALT > 5x ULN	2/1229 (0.2%)	0/474	3/1919 (0.2%)	3/2430 (0.1%)
ALT > 10x ULN	0/1229	0/474	0/1919	0/2430
ALT > 20x ULN	0/1229	0/474	0/1919	0/2430
AST > 3x ULN	2/1362 (0.1%)	1/522 (0.2%)	3/2139 (0.1%)	4/2700 (0.1%)
AST > 5x ULN	1/1362 (<0.1%)	1/522 (0.2%)	0/2139	1/2700 (<0.1%)
AST > 10x ULN	0/1362	0/522	0/2139	0/2700
AST > 20x ULN	0/1362	0/522	0/2139	0/2700
Total bilirubin > 2x ULN	0/1332	0/480	0/2149	0/2629

41 Hy's Law: (1)The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.
(2) Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN). (3) No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Final, July 2009

	Placebo N=1515	NB16 N=633	NB32 N=2545	Total N=3239
Hy's Law 1: ALT >3 x ULN and bilirubin >2 x ULN	0/1338	0/487	0/2163	0/2650
Hy's Law 2: AST >3 x ULN and bilirubin >2 x ULN	0/1338	0/487	0/2163	0/2650

Gallbladder-related SAEs occurred in 0.3% of subjects in the Total NB group and <0.1% in the placebo group. All Gallbladder-related SAE subjects were hospitalized and underwent gallbladder surgery.

This reviewer did additional analyses which confirmed that there were few subjects in either group with hepatic events.

6.3.4.9. Hypersensitivity Reaction/Skin Rash

The Hypersensitivity Reaction/Skin Rash special topic consisted of the following subtopics, categories, and preferred terms are listed in Appendix D6.

The incidence of Hypersensitivity Reaction/Skin Rash events was similar in the Total NB group compared with the placebo group (13.4% and 15.2%, respectively) in the Primary Dataset and there was no difference in the incidence of SAEs (≤0.1% in both groups).

Table 61: Incidence of Hypersensitivity Reaction/Skin Rash Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Hypersensitivity Reaction/Skin Rash TEAEs	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Subjects with Any TEAE	**231 (15.2%)**	**434 (13.4%)**
Systemic reactions	161 (10.6%)	271 (8.4%)
Anaphylaxis/angioedema	6 (0.4%)	18 (0.6%)
Potential allergic symptoms	156 (10.3%)	257 (7.9%)
Skin Reactions	81 (5.3%)	187 (5.8%)
Local Reactions	9 (0.6%)	15 (0.5%)
Subjects with any treatment-emergent SAE	**2 (0.1%)**	**3(<0.1%)**
Systemic reactions	2 (0.1%)	3(<0.1%)
Anaphylaxis/angioedema	1 (<0.1%)	0
Potential allergic symptoms	1 (<0.1%)	3(<0.1%)
Skin Reactions	0	0
Local Reactions	0	0
Subjects discontinued due to AE	**81(1.2%)**	**60 (1.9%)**
Systemic reactions	7 (0.5%)	9 (0.3%)
Anaphylaxis/angioedema	1 (<0.1%)	2 (<0.1%)

Hypersensitivity Reaction/Skin Rash TEAEs	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Potential allergic symptoms	6 (0.4%)	7 (0.2%)
Skin Reactions	11 (0.7%)	51 (1.6%)
Local Reactions	0	0

Data Source: Applicant's Tables ISS.P.SKN.1-1, ISS.P.SKN.2-1, and ISS.P.SKN.3-1.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48

Systemic Reactions

Events in the Systemic Reactions subtopic occurred at a similar incidence in the Total NB group compared with the placebo group (8.4% and 10.6%, respectively). The incidence of events in the Anaphylaxis/Angioedema category (Total NB 0.6%, placebo 0.4%) and the Potential Allergic Symptoms category (Total NB 7.9%, placebo 10.3%) was also similar. Oropharyngeal pain (Total NB 2.8%, placebo 3.4%) and cough (Total NB 2.6%, placebo 3.3%) were the most frequent preferred terms in the Potential Allergic Symptoms category. There were no events of eosinophilic pneumonia reported.

There were a total of five SAEs in the Systemic Reactions subtopic (2 placebo subjects, three NB32 subjects, no NB16 subjects). Of the placebo subjects, one (066-NB-304-033) experienced an anaphylactic reaction to a sulfa drug and the other (051-NB-301-050) had chest discomfort (verbatim: non-cardiac chest discomfort). Of the three subjects on NB32:

- (019-NB-303-053) had an event of bronchospasm following accidentally inhaling smoke from burning food on the stove
- (033-NB-302-131) had events of acute bronchitis and asthma (verbatim: exacerbation of asthma). This subject had a history of seasonal allergy, asthma and sinusitis and continued study drug to completion of the trial
- (098-NB-301-057) had an event of dyspnea. This subject had a history of asthma, cardiac hypertrophy, atrial fibrillation and of a previous hospitalization for shortness of breath which did not reveal an etiology despite an extensive work up which included a lung biopsy. This subject did not return to the clinical study site after being released from the hospital in improved condition.

Anaphylaxis/angioedema discontinuations occurred in one subject in the placebo group who developed a swollen tongue (Day 89) following oral mucosal blistering (Day 83), one subject in the NB16 group who experienced angioneurotic edema (verbatim: giant urticaria rash generalized, Day 19) and one subject in the NB32 group who experienced lip swelling (Day 27).

In the Potential Allergic Symptoms category, four discontinued due to dyspnea (one in the NB16 group and three in the NB32 group including one SAE, 098-NB-301-057), six due to chest discomfort (four placebo subjects and one each in the NB16 and NB32 groups), one due to hypersensitivity (NB32 group), one due to generalized edema (placebo group) and one due to edema peripheral (placebo group).

6.4 Supportive Safety Results

6.4.1 Common Adverse Events

Common AEs are defined by Orexigen as AEs that occurred at a ≥5% incidence in any group. Treatment-emergent adverse events (TEAEs) are defined as events that occurred or worsened on or after the date of first dose until 7 days after the last confirmed dose.

During the double-blind treatment phase, the common (≥5% incidence) TEAEs in the Total NB group that occurred at least twice the incidence of placebo were nausea, constipation, vomiting, dizziness, and dry mouth. Other TEAEs of interest (those that occurred at a ≥2% incidence in the Total NB group and at least twice the incidence of placebo) were tremor, hot flush, tinnitus, abdominal pain upper, dysgeusia, hyperhidrosis, and palpitations.

Table 62: Treatment-Emergent Adverse Events: Primary Dataset, Double-Blind Treatment Phase

Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Adverse Events at a ≥5% Incidence in Any Group				
Subjects with any TEAE	**1137 (75.0%)**	**507 (80.1%)**	**2221 (87.3%)**	**2769 (85.5%)**
Nausea	102 (6.7%)	175 (27.6%)	828 (32.5%)	1030 (31.8%)
Constipation	109 (7.2%)	95 (15.0%)	489 (19.2%)	587 (18.1%)
Headache	157 (10.4%)	98 (15.5%)	447 (17.6%)	554 (17.1%)
Vomiting	44 (2.9%)	41 (6.5%)	273 (10.7%)	321 (9.9%)
Dizziness	51 (3.4%)	52 (8.2%)	252 (9.9%)	311 (9.6%)
Insomnia	89 (5.9%)	42 (6.6%)	233 (9.2%)	277 (8.6%)
Upper respiratory tract infection	152 (10.0%)	50 (7.9%)	208 (8.2%)	258 (8.0%)
Dry mouth	35 (2.3%)	47 (7.4%)	205 (8.1%)	256 (7.9%)
Nasopharyngitis	124 (8.2%)	36 (5.7%)	180 (7.1%)	218 (6.7%)
Diarrhea	79 (5.2%)	33 (5.2%)	180 (7.1%)	215 (6.6%)
Sinusitis	94 (6.2%)	(6.2%)	118 (4.6%)	159 (4.9%)
Adverse Events at a ≥2% Incidence in the Total NB group and at least 2X the Incidence of Placebo				
Tremor	10 (0.7%)	23 (3.6%)	103 (4.0%)	126 (3.9%)
Hot flush	18 (1.2%)	16 (2.5%)	108 (4.2%)	124 (3.8%)
Tinnitus	9 (0.6%)	27 (4.3%)	83 (3.3%)	110 (3.4%)
Abdominal pain upper	20 (1.3%)	13 (2.1%)	88 (3.5%)	102 (3.1%)
Dysgeusia	10 (0.7%)	14 (2.2%)	61 (2.4%)	77 (2.4%)
Hyperhidrosis	9 (0.6%)	10 (1.6%)	65 (2.6%)	77 (2.4%)
Palpitations	13 (0.9%)	22 (3.5%)	54 (2.1%)	77 (2.4%)

Data Source: Applicant's Table ISS.P.6.1-3.1.
Events are listed in decreasing order of incidence based on the Total NB group.

Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48; TEAE=treatment-emergent adverse event.				

Infrequent Treatment-Emergent Adverse Events: Primary Dataset
To examine less frequent events, which may be medically important or show a meaningful increase in frequency in NB-treated subjects compared to placebo subjects, the following thresholds were chosen by the applicant based on the sample sizes in the Total NB and placebo groups (3239 and 1515 subjects, respectively). These less frequent events were then reviewed for medical importance and included based on clinical judgment.

- ≥0.2% and <2% and at least 7 subjects in the Total NB group and at least twice the incidence of the placebo group (0.2% Total NB = 5 to 8 subjects; 0.1% placebo = 1 to 2 subjects)
- 6 subjects in the Total NB group and 0 or 1 in the placebo group
- 5 subjects in the Total NB group (or fewer based on clinical judgment) and 0 in the placebo group

Medically important events occurring at an increased frequency in the Total NB group compared to placebo are listed below by SOC. Events due to external factors (arthropod sting, food poisoning, etc.) were excluded along with preferred terms that are medically related to more common terms where no increase in frequency was seen (e.g., respiratory tract infection vs. nasopharyngitis).

Cardiac Disorders: myocardial infarction, tachycardia
Ear and Labyrinth Disorders: motion sickness, vertigo
Gastrointestinal Disorders: abdominal pain lower, eructation, hematochezia, hernia, lip swelling
General Disorders and Administration Site Conditions: asthenia, feeling abnormal, feeling hot, feeling jittery, thirst
Hepatobiliary Disorders: cholecystitis
Infections and Infestations: kidney infection, pneumonia, staphylococcal infection
Investigations: AST increased, blood creatinine increased, hematocrit decreased, hepatic enzymes increased
Metabolism and Nutrition Disorders: dehydration
Musculoskeletal and Connective Tissue Disorders: intervertebral disc protrusion, pain in jaw
Nervous System Disorders: amnesia, balance disorder, disturbance in attention, intention tremor, lethargy, memory impairment, mental impairment, presyncope
Psychiatric Disorders: abnormal dreams, agitation, dissociation (verbatim term: typically "feeling spacey"), mood swings, nervousness, tension
Renal and Urinary Disorders: micturition urgency
Reproductive System and Breast Disorders: erectile dysfunction, menstruation irregular, vaginal hemorrhage, vulvovaginal dryness

Skin and Subcutaneous Tissue Disorders: alopecia, erythematous rash

Table 63: Infrequent Treatment-Emergent Adverse Events: Primary Dataset

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Double-Blind Treatment Phase				
Subjects with any TEAE	**1137 (75.0%)**	**507 (80.1%)**	**2221 (87.3%)**	**2769 (85.5%)**
Cardiac Disorders	**38 (2.5%)**	**31 (4.9%)**	**93 (3.7%)**	**125 (3.9%)**
Myocardial infarction	0	0	3 (0.1%)	3 (<0.1%)
Tachycardia	2 (0.1%)	4 (0.6%)	16 (0.6%)	20 (0.6%)
Ear & Labyrinth Disorders	**23 (1.5%)**	**37 (5.8%)**	**148 (5.8%)**	**187 (5.8%)**
Motion sickness	1 (<0.1%)	3 (0.5%)	13 (0.5%)	
Vertigo	4 (0.3%)	0	1 (<0.1%)	1 (<0.1%)
Gastrointestinal Disorders	**409 (27.0%)**	**310 (49.0%)**	**1454 (57.1%)**	**1794 (55.4%)**
Abdominal pain lower	2 (0.1%)	1 (0.2%)	9 (0.4%)	10 (0.3%)
Hernia (umbilical, abdominal)	0	0	8 (0.3%)	8 (0.2%)
Eructation	1 (<0.1%)	2 (0.3%)	6 (0.2%)	8 (0.2%)
Hematochezia	1 (<0.1%)	0	6 (0.2%)	6 (0.2%)
Lip swelling	0	1 (0.2%)	6 (0.2%)	7 (0.2%)
General Disorders & Administration Site Conditions	**185 (12.2%)**	**75 (11.8%)**	**399 (15.7%)**	**481 (14.9%)**
Asthenia	1 (<0.1%)	3 (0.5%)	18 (0.7%)	21 (0.6%)
Feeling abnormal	2 (0.1%)	3 (0.5%)	20 (0.8%)	24 (0.7%)
Feeling hot	0	2 (0.3%)	4 (0.2%)	6 (0.2%)
Feeling jittery	5 (0.3%)	3 (0.5%)	36 (1.4%)	41 (1.3%)
Thirst	1 (<0.1%)	0	8 (0.3%)	8 (0.2%)
Hepatobiliary Disorders	**9 (0.6%)**	**5 (0.8%)**	**24 (0.9%)**	**29 (0.9%)**
Cholecystitis	2 (0.1%)	0	9 (0.4%)	9 (0.3%)
Infections & Infestations	**570 (37.6%)**	**201 (31.8%)**	**888 (34.9%)**	**1101 (34.0%)**
Kidney Infection	0	1 (0.2%)	5 (0.2%)	6 (0.2%)
Pneumonia	4 (0.3%)	4 (0.6%)	16 (0.6%)	20 (0.6%)
Staphylococcal infection	1 (<0.1%)	1 (0.2%)	6 (0.2%)	7 (0.2%)
Investigations	**101 (6.7%)**	**32 (5.1%)**	**206 (8.1%)**	**238 (7.3%)**
AST increased	2 (0.1%)	0	13 (0.5%)	13 (0.4%)
Blood creatinine increased	2 (0.1%)	13 (0.4%)	15 (0.6%)	17 (0.5%)
Hematocrit decreased	0	0	5 (0.2%)	5 (0.2%)
Hepatic enzymes increased	1 (<0.1%)	2 (0.3%)	5 (0.2%)	7 (0.2%)
Metabolism & Nutrition Disorders	**81 (5.3%)**	**14 (2.2%)**	**112 (4.4%)**	**126 (3.9%)**
Dehydration	1 (<0.1%)	1 (0.2%)	6 (0.2%)	7 (0.2%)
Musculoskeletal and Connective Tissue Disorders	**281 (18.5%)**	**84 (13.3%)**	**395 (15.5%)**	**485 (15.0%)**
Intervertebral disc protrusion	0	0	8 (0.3%)	8 (0.2%)
Pain in jaw	0	1 (0.2%)	5 (0.2%)	6 (0.2%)
Nervous System Disorders	**287 (18.9%)**	**195 (30.8%)**	**901 (35.4%)**	**1115 (34.4%)**
Amnesia	2 (0.1%)	0	11 (0.4%)	11 (0.3%)
Balance disorder	2 (0.1%)	0	14 (0.6%)	14 (0.4%)
Disturbance in attention	5 (0.3%)	6 (0.9%)	39 (1.5%)	45 (1.4%)
Intention tremor	3 (0.2%)	1 (0.2%)	18 (0.7%)	19 (0.6%)
Lethargy	4 (0.3%)	5 (0.8%)	26 (1.0%)	31 (0.5%)
Memory Impairment	3 (0.2%)	3 (0.5%)	9 (0.4%)	13 (1.0%)
Presyncope	0	0	6 (0.2%)	6 (0.2%)

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Psychiatric Disorders	**213 (14.1%)**	**86 (13.6%)**	**517 (20.3%)**	**608 (18.8%)**
Abnormal dreams	6 (0.4%)	4 (0.6%)	25 (1.0%)	29 (0.9%)
Agitation	1 (<0.1%)	0	8 (0.3%)	8 (0.2%)
Dissociation/"feeling spacey"	0	0	10 (0.4%)	10 (0.3%)
Mood swings	1 (<0.1%)	1 (0.2%)	6 (0.2%)	7 (0.2%)
Nervousness	2 (0.1%)	3 (0.5%)	13 (0.5%)	18 (0.6%)
Tension	2 (0.1%)	0	10 (0.4%)	10 (0.3%)
Renal and Urinary Disorders	**17 (1.1%)**	**5 (0.8%)**	**40 (1.6%)**	**45(1.4%)**
Micturition urgency	0	0	5 (0.2%)	5 (0.2%)
Reproductive System and Breast Disorders	**43 (2.8%)**	**10 (1.6%)**	**111 (4.4%)**	**125 (<3.9%)**
Erectile dysfunction	1 (<0.1%)	0	6 (0.2%)	6 (0.2%)
Menstruation irregular	4 (0.3%)	3 (0.5%)	15 (0.6%)	18 (0.6%)
Vaginal hemorrhage	0	1 (0.2%)	6 (0.2%)	7 (0.2%)
Vulvovaginal dryness	1 (<0.1%)	0	5 (0.2%)	6 (0.2%)
Skin & Subcutaneous Tissue Disorders	**148 (9.8%)**	**67 (10.6%)**	**333 (13.1%)**	**409 (12.6%)**
Alopecia	11 (0.7%)	8 (1.3%)	46 (1.8%)	55 (1.7%)
Erythematous rash	0	2 (0.3%)	5 (0.2%)	7 (0.2%)

Data Source: Applicant's Table ISS.P.6.1-3.5.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48; TEAE=treatment-emergent adverse event.

Severity

The majority of TEAEs reported during the double-blind treatment phase were assessed by the study investigator as mild to moderate in severity. A higher percentage of subjects in the Total NB group experienced a severe TEAE than those in the placebo group (11.8% vs. 6.9%).[42] Events with a missing severity rating were categorized as severe.

Due to the low incidence of severe events, the applicant chose a cut-off of ≥0.4% in the Total NB group (at least 12 subjects) and at least twice the incidence of placebo was chosen to identify clinically meaningful differences between treatments. Severe TEAEs that occurred at an incidence of ≥0.4% in the Total NB group and at least twice the incidence of placebo (in decreasing order of frequency) were nausea, headache, vomiting, constipation, dizziness, abdominal pain upper, migraine, and insomnia; the only severe TEAE that occurred at an incidence of ≥0.4% in the placebo group was sinusitis.

42 In Orexigen's Advisory Committee briefing document they report the incidence of severe AEs as 13.8% for Total NB and 9.2% for placebo. These calculations are based on the number of patients with adverse events as the denominator for each treatment group. The percentages in the FDA briefing document used the total number of patients in the primary safety analysis set in each treatment as the denominator.

Table 64: Treatment-Emergent Adverse Events by Maximum Severity and Severe Events (≥0.4% Total NB and at Least Twice the Incidence of Placebo): Primary Dataset, Double-Blind Treatment Phase

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Subjects with any TEAE	**1137 (75.0%)**	**507 (80.1%)**	**2221 (87.3%)**	**2769 (85.5%)**
Mild	479 (31.6%)	217 (34.3%)	800 (31.4%)	1040 (32.1%)
Moderate	553 (36.5%)	232 (36.7%)	1100 (43.2%)	1347 (41.6%)
Severe	105 (6.9%)	58 (9.2%)	321 (12.6%)	382 (11.8%)
Severe TEAE				
Gastrointestinal Disorders	**14 (0.9%)**	**19 (3.0%)**	**108 (4.2%)**	**128 (4.0%)**
Nausea	1 (<0.1%)	10 (1.6%)	53 (2.1%)	63 (1.9%)
Constipation	2 (0.1%)	4 (0.6%)	16 (0.6%)	20 (0.6%)
Vomiting	5 (0.3%)	3 (0.5%)	19 (0.7%)	22 (0.7%)
Abdominal pain upper	3 (0.2%)	3 (0.5%)	10 (0.4%)	14 (0.4%)
Nervous System Disorders	**12 (0.8%)**	**13 (2.1%)**	**68 (2.7%)**	**82 (2.5%)**
Headache	5 (0.3%)	7 (1.1%)	28 (1.1%)	35 (1.1%)
Dizziness	3 (0.2%)	4 (0.6%)	14 (0.6%)	18 (0.6%)
Migraine	2 (0.1%)	0	11 (0.4%)	12 (0.4%)
Psychiatric Disorders	**5 (0.3%)**	**3 (0.5%)**	**28 (1.1%)**	**32 (1.0%)**
Insomnia	1 (<0.1%)	2 (0.3%)	25 (1.0%)	14 (0.4%)

Data Source: Applicant's Table ISS.P.6.1-313.
TEAEs were defined as events that first occurred or worsened during the double-blind treatment phase (first dose date ≤ AE onset date ≤ last confirmed dose date + 7 days [excluding AEs that occurred during the drug discontinuation or extension phase]). Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48; TEAE=treatment-emergent adverse event.
For subjects with multiple events within the same preferred term or body system, only the most severe event was reported. Missing severity was assumed as 'severe'.

Titration Phase:
There was a difference in incidence of TEAEs between the Total NB and placebo groups during the titration phase. During the titration phase, 62.5% of subjects in the Total NB group reported at least one TEAE compared with 37.2% of subjects in the placebo group. During the titration phase, the common (≥5% incidence) TEAEs in the Total NB group that occurred at least twice the incidence of placebo (nausea, constipation, vomiting, dizziness, and dry mouth) were previously identified during the double-blind treatment phase. However, two other common TEAEs, headache and insomnia, were identified during the titration phase and not previously noted in the double-blind treatment phase. Other TEAEs of interest during the titration phase (those that occurred at a ≥2% incidence in the Total NB group and at least twice the incidence of placebo) included tremor, hot flush, and tinnitus and anxiety.

SUMMARY

Most frequently reported TEAEs in the Total NB group:
Nausea, constipation, vomiting, dizziness, dry mouth, headache and insomnia were the most frequently reported TEAEs in the Total NB group. Of these 7 events, nausea was the most frequently reported TEAE in the Total NB group during the entire 56-week double-blind treatment phase (31.8% vs. 6.7% for placebo) as well as during the titration phase (24.8% vs. 4.0% for placebo) and maintenance phase (9.9% vs. 3.0% for placebo).

Nausea: No TEAE of nausea was considered serious; it was considered severe in 1.9% of subjects in the Total NB group (compared with <0.1% of subjects in the placebo group). A total of 6.3% of subjects in the Total NB group discontinued treatment due to nausea (compared with 0.2% of subjects in the placebo group).

Constipation: No events were considered serious. The incidence of severe constipation during double-blind treatment was greater for Total NB (0.6%) than placebo (0.1%) as was the incidence of treatment discontinuations due to constipation (0.4% vs. <0.1%).

Vomiting: No events were considered serious. The incidence of severe vomiting during double-blind treatment was greater for Total NB (0.7%) than placebo (0.3%) as was the incidence of treatment discontinuations due to vomiting (1.1% vs. <0.1%).

Dizziness: One subject in the placebo group (<0.1%) reported a serious event. The incidence of severe dizziness during double-blind treatment was greater for Total NB (0.6%) than placebo (0.2%) as was the incidence of treatment discontinuations due to dizziness (1.3% vs. 0.3%).

Dry mouth: No events were considered serious. Severe dry mouth and treatment discontinuations due to dry mouth during double-blind treatment were rare for both Total NB and placebo (<0.1% vs. 0% and 0.1% vs. 0%, respectively).

Headache: No events were considered serious. The incidence of severe headache during double-blind treatment was greater for Total NB (1.1%) than placebo (0.3%) as was the incidence of treatment discontinuations due to headache (1.7% vs. 0.6%).

Insomnia: No events were considered serious. Severe insomnia and treatment discontinuations due to insomnia during double-blind treatment were rare for both Total NB and placebo (0.4% vs. <0.1% and 0.7% vs. 0.5%, respectively).

These seven AEs are consistent with the labeled AE profiles of both naltrexone and bupropion.

Severe TEAEs that occurred at an incidence of ≥0.4% (a lower cutoff was chosen due to the low incidence of severe events) in the Total NB group and at least twice the incidence of placebo were nausea, headache, vomiting, constipation, dizziness, abdominal pain upper, migraine, and insomnia in the double-blind treatment phase.

Based on the analyses of TEAEs in the Diabetic and Nondiabetic Datasets, insomnia, hypertension, and anxiety were identified as common TEAEs and at least twice the incidence of the placebo in overweight and obese subjects with diabetes, in addition to events commonly seen in the Nondiabetic Dataset. Blood pressure-related TEAEs (including hypertension and increased blood pressure terms) in both the NB32 and placebo groups were reported mostly by subjects with a history of hypertension or antihypertensive medication use at baseline, occasionally led to treatment discontinuation, and required medication in approximately two-thirds of subjects. In Trial NB-304, 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. Four out of the 40 subjects (10%) in the NB32 group who had a blood pressure-related TEAE experienced a severe blood pressure-related TEAE, one of which led to discontinuation of study drug. No placebo subject with a blood-pressure-related TEAE had a severe event. No blood pressure-related AE was considered serious in either treatment group.

6.4.2 Electrocardiograms (ECGs)

Clinically significant ECG abnormalities were recorded as AEs and are discussed in *Section 6.3.4.2. Cardiovascular Events*.

Orexigen performed a QT analysis using data from a Phase 1 (NB-228) and Phase 3 (NB-303) trials which showed that large changes in QTc intervals were not observed.

From baseline to endpoint, mean values in the Total NB group for ventricular rate, and PR, QRS, QT, and QTcF intervals were similar to those in the placebo group. The mean maximum value and change from baseline to maximum at any time during the trial for PR and QRS intervals were similar between the Total NB and placebo groups. Overall, there were no clinically relevant differences between the Total NB and the placebo groups and no evidence of either an NB or dose effect for any parameter.

Mean maximum values and mean change from baseline to maximum were higher for ventricular rate in the Total NB group compared with placebo (mean change: 4.62 bpm vs. 2.24 bpm, respectively) and lower for QTcF interval in the Total NB group compared with placebo (mean change: 3.20 msec vs. 6.24 msec, respectively).

Categorical ECG Interval Analysis
Categorical analysis of subjects with normal measurements at baseline showed that 0.1% of subjects in both groups had a QTcF interval > 480 msec, no subjects had a QTcF interval >500 msec at any time during the trial, and <1% of subjects had a QTcF increase from baseline of ≥60 msec (0.6% Total NB vs. 0.4% placebo). A QRS interval >110 msec was infrequent in both the Total NB and placebo groups (2.8% and 1.9%, respectively). The incidence of a low PR interval (<120 msec) or a high PR interval (>200 msec and increase >20 msec from baseline) was low and similar between the Total NB (2.0% and 1.1%, respectively) and placebo (2.6% and 1.3%, respectively) groups. These ECG results are consistent with a lack of study drug effect on ECG parameters.

Categorical analysis of ECG measurements in the Diabetic vs the Nondiabetic Dataset showed that the incidence of treatment-emergent changes in ECG results were higher for the Diabetic Dataset compared with the Nondiabetic Dataset in both the Total NB and placebo groups for all other prespecified criteria. Greater incidences of QTcF values >450 ms were observed in the Diabetic Dataset in both the NB32 and placebo groups (3.0% and 4.1%, respectively) compared with the Nondiabetic Dataset (2.6% and 3.4%, respectively). Greater incidences of QTcF values ≥30 msec from baseline were observed in the Diabetic Dataset in both the NB32 and placebo

groups (9.3% and 7.7%, respectively) compared with the Nondiabetic Dataset (4.5% and 5.7%, respectively). Thus, within the Diabetic Dataset the incidence in QTcF ≥30 ms was slightly higher in the NB32 arm compared to the placebo arm. Greater incidences of QTcF values ≥60 ms from baseline were also observed in the Diabetic Dataset in both the NB32 and placebo groups (1.5% and 1.2%, respectively) compared with the Nondiabetic Dataset (0.4% and 0.2%, respectively).

6.5 Other Safety Explorations

6.5.1 Time Dependency for Adverse Events

Time to Onset and Resolution for Selected Events (Nausea, Constipation, Headache, Vomiting, Dizziness, Anxiety, Hypertension, and Depression) is described in Appendix E.

6.5.2 Drug-Demographic Interactions

Gender:

- In the Total NB group, females had a higher overall incidence of AEs leading to discontinuation compared with males (25.2% vs. 16.9%, respectively). Common AEs leading to discontinuation that occurred at a higher incidence in females compared with males in the Total NB group were nausea (7.0% vs. 2.6%), vomiting (1.2% vs. 0.7%), and dizziness (1.4% vs. 0.7%).
- Events of hypertension were reported with disproportionate frequency for males vs. females compared to the distribution of the enrolled population for both Placebo and NB populations.
- In the Total NB group, the incidence of TEAEs was higher in females compared with males for Gastrointestinal Disorders (57.5% vs. 45.0%); Nervous System Disorders (35.5% vs. 29.3%); and Skin and Subcutaneous Tissue Disorders (13.5% vs. 8.4%). In both the Total NB and placebo groups, the incidence of TEAEs was higher in males compared with females for Musculoskeletal and Connective Tissue Disorders (22.8% vs. 13.4% for Total NB, and 22.8% vs. 17.6% for placebo, respectively. With regard to the common TEAEs, in the Total NB group, nausea and headache occurred at a higher incidence in females (34.3% and 18.1%, respectively) compared with males (19.7% and 12.4%, respectively).

Age:

- Within the NB group, AEs leading to discontinuation were higher in the >65 age group and AEs were higher in the NB group as compared to the placebo group across all age groups: 18-44: 21.2%; 45-64: 25.4%; ≥ 65: 38.7%.
- Hypertension events for both NB-treated and placebo subjects were disproportionately represented among subjects aged 45-64 years versus younger subjects.

- Subjects ≥65 years of age in the Total NB group experienced more Psychiatric Disorders SOC events (27.4%) compared to placebo (6.3%) although the sample size was small (62, 32) for Total NB and placebo, respectively. The majority of events were due to insomnia (11.3% Total NB, 3.1% placebo) and depression (6.5% Total NB, 3.1% placebo).
- There was a higher incidence of dizziness, tremor, and hypertension in the subjects ≥65 years compared with the 18-44 and 45-64 years subgroups—particularly in the subjects on NB therapy.

Race:

- In the Total NB group, the incidence of AEs leading to discontinuation was somewhat higher in 'Other' (non-White or non-Black/African American) and Blacks/African-Americans compared with Whites (31.8%, 27.5%, vs. 22.4%, respectively).
- Among the subjects experiencing hypertension events, a greater proportion were Black/African American in the NB-treated group (26.0%) compared to the placebo-treated group (11.7%).

6.5.3 Drug-Disease Interactions

Antihypertensive Medication Status:

- The overall incidence of TEAEs was higher in subjects taking antihypertensive medication compared with subjects not taking antihypertensive medication in the Total NB group (89.0% vs. 84.3%, respectively) with a greater difference in the placebo group (82.5% vs. 72.8%, respectively).
- Hypertension occurred at a higher incidence in the Total NB group in subjects using antihypertensive medication (6.9%) compared with subjects not using antihypertensive medication (1.6%); a similar trend was observed in the placebo group (4.5% vs. 1.6%).

Diabetes:

- In the double-blind treatment phase, 13 of 333 (3.9%) NB32 and 8 of 169 (4.7%) placebo subjects in the Diabetic Dataset experienced an SAE, compared with 51 of 2212 (2.3%) NB32 and 17 of 1346 (1.3%) placebo subjects in the Nondiabetic Dataset.
- In the NB32 group, a higher percentage of subjects who had diabetes discontinued treatment due to nausea and vomiting than subjects who did not have diabetes (9.6% vs. 5.8% and 3.0% vs. 0.8%, respectively).
- In the analysis of the diabetic subjects, a higher percentage of NB subjects experienced shifts to high creatinine as compared to placebo subjects (12.7% NB vs 3.1% placebo).

6.6 Additional Safety Evaluations

6.6.1 Human Carcinogenicity

Carcinogenicity studies were conducted under both NDA 18-932 (ReVia®) and NDA 20-358 (Wellbutrin SR®) supporting the chronic indication of Contrave.

- In a two-year carcinogenicity study in rats with naltrexone[43], there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day was 4%, but only the incidence in females was increased compared with a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a two-year dietary study with naltrexone in male and female mice.
- Lifetime carcinogenicity studies of bupropion[44] were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study. Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenetic studies.

Neoplasms developed infrequently in the Phase 3 clinical trials and were from a variety of sites. There were 3 cases (0.2%) of neoplasm in the placebo group and 5 cases (0.2%) in the Total NB group.

Table 65: Incidence of Neoplasms Across Treatment Groups: Primary Dataset

System Organ Class Preferred Term	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Double-Blind Treatment Phase				
Neoplasms Benign, Malignant, and Unspecified	**3 (0.2%)**	**1 (0.2%)**	**4 (0.2%)**	**5 (0.2%)**
Breast cancer in situ	0	1 (0.2%)	0	1 (<0.1%)
Breast cancer	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Colon cancer	0	0	1 (<0.1%)	1 (<0.1%)
Meningioma	0	0	1 (<0.1%)	1 (<0.1%)
Multiple myeloma	0	0	1 (<0.1%)	1 (<0.1%)
Oesophageal carcinoma	1 (<0.1%)	0	0	0
Uterine leiomyoma	1 (<0.1%)	0	0	0

6.6.2 Human Reproduction and Pregnancy Data

Reproduction and developmental studies have not been conducted with NB; although studies in pregnant rats and rabbits have been conducted with naltrexone and bupropion separately.

43 Listed Drug Label: ReVia (naltrexone hydrochloride tablets)
44 Listed Drug Label: Wellbutrin SR (bupropion hydrochloride) Sustained- Release Tablets

Naltrexone[45]: Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses 5 times the recommended therapeutic dose, based on body surface area) and to rabbits at oral doses 18 times the recommended therapeutic dose, based on body surface area). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 32 and 65 times the recommended therapeutic dose, respectively, based on body surface area.

Bupropion[46]: In studies conducted in rats and rabbits, bupropion was administered orally at doses approximately 11 and 7 times the MRHD, respectively, on a mg/m^2 basis, during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater. When rats were administered bupropion at oral doses of up to approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

One study of bupropion has been conducted in pregnant women. This retrospective, managed-care database study assessed the risk of congenital malformations overall and cardiovascular malformations specifically, following exposure to bupropion in the first trimester compared to the risk of these malformations following exposure to other antidepressants in the first trimester and bupropion outside of the first trimester. This study included 7,005 infants with antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study showed no greater risk for congenital malformations overall or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated.

A recent report by Alwan et al.[47] summarized the results of a retrospective case-control study of birth defect risk factors to evaluate whether maternal bupropion treatment in early pregnancy may be associated with congenital heart defects. Data on 6853 infants with major heart defects were compared with 5869 control infants born in 1997-2004. Bupropion exposure was defined as any reported use between 1 month before and 3 months after conception. Mothers of infants with left outflow tract heart defects were more likely to have reported taking bupropion than mothers of control infants (adjusted odds ratio, 2.6; 95% confidence interval, 1.2-5.7; P = .01).

45 Naltrexone Hydrochloride Tablet, http://dailymed nlm nih.gov/dailyme
46 Wellbutrin SR: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
47 Alwan S, Reefhuis J, Botto LD, Rasmussen SA, Correa A, Friedman JM, National Birth Defects Prevention Study. Maternal use of bupropion and risk for congenital heart defects. Am J Obstet Gynecol. 2010 Apr 22 [Epub ahead of print].

At The Motherisk Program, Einarson et al.[48] analyzed pregnancy outcomes of women *(n* = 1243) from prospectively collected cases in their database, who were exposed to antidepressants during their pregnancy. The authors compared them with a matched comparison group of women *(n* = 1243) who were not exposed (nonteratogen group). Women *(n* = 928) who fit the criteria for inclusion, were exposed in the first trimester of pregnancy, and gave birth to a live-born infant were matched to women *(n* = 928) in the comparison group. There were 30 (3.2%) major malformations in the antidepressant group and 31 (3.3%) in the comparison group (OR 0.9; 95% CI 0.5 to 1.61). The antidepressants included in the analysis were: bupropion (113), citalopram (184), escitalopram (21), fluvoxamine (52), nefazodone (49), paroxetine (148), mirtazepine (68), fluoxetine (61), trazodone (17), venlafaxine (154), and sertraline (61). The authors concluded that, as a group, antidepressant use in the first trimester of pregnancy is not associated with an increased risk for major malformation above the baseline. In addition, no individual antidepressant was associated with an increased risk of a specific malformation.

In the NB clinical development program, 29 women became pregnant (21/3024 NB subjects, 7/1247 placebo subjects, 1 fluoxetine/naltrexone subject from the OT-101 study). Of the 21 subjects who became pregnant after receiving naltrexone and bupropion in combination, one subject received a single dose of naltrexone SR 16 mg/ bupropion SR 180 mg (as part of Study NB-229), two received NB16 (for up to 161 days), 16 received NB32 (for up to 396 days), and two subjects in Trial NB-303 received NB48 (for up to approximately 167 days) following re-randomization after receiving NB32 for up to approximately 241 days. One subject in Study OT-101 received fluoxetine 60 mg/naltrexone 50 mg for 166 days.

Of the 21 NB subjects who became pregnant, 11 carried to term and gave birth to a healthy infant, three had elective abortions, four subjects experienced spontaneous abortions, and the outcomes of 2 pregnancies were unknown. One additional NB32/48 subject, 065-NB-303-051, reported that she was no longer pregnant approximately 2 months after her positive pregnancy test; however, she did not provide additional details about the outcome of the pregnancy. There were no reports of congenital anomaly.

6.6.3 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose: No overdose events occurred in the NB development program. Overdoses of up to 30 g or more of bupropion have been reported in the Wellbutrin SR prescribing information. Seizure was reported in approximately one third of all cases. A 3-year multi–poison center observational study[49] of hospitalized patients with ingestion of bupropion XL ≥600 mg in adults and ≥4 mg/kg in children demonstrated that seizures occurred in 32% patients, with initial seizure at 0.5 to 24 hours after ingestion; 32% patients had initial seizure at > 8 hours. Subsequent seizures occurred in 49%. In patients ≥ 13 years of age, median dose with seizures was 4350 mg (range, 600-54

48 Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. Can J Psychiatry. 2009 Apr;54(4):242-246.

49 Starr P, Klein-Schwartz W, Spiller H, Kern P, Ekleberry SE, Kunkel S. Incidence and onset of delayed seizures after overdoses of extended-release bupropion. Am J Emerg Med. 2009 Oct;27(8):911-915.

000) compared to 2400 mg (range, 600-9000) in patients without seizures. Agitation, tremors, and hallucinations occurred in 29.7%, 40.5%, and 18.9% of patients with seizures, respectively, compared with 12.5 %, 17.5%, and 10% in patients without seizures. The neurologic effects agitation (P = .045) and tremors (P = .005) occurred more frequently.

Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses. Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

There is limited experience with overdose of naltrexone monotherapy. In one study, subjects who received 800 mg daily of naltrexone hydrochloride for up to one week showed no evidence of toxicity (naltrexone hydrochloride prescribing information).

Drug Abuse: Naltrexone labeling states that the drug is a pure opioid antagonist that does not lead to physical or psychological dependence, and that tolerance to naltrexone is not known to occur. The bupropion labeling cites data from clinical trial subjects and healthy volunteers suggesting evidence of increases in motor activity and agitation/excitement, and from a laboratory study in drug abusers at a dose of 400 mg which resulted in findings of mild amphetamine-like activity.

7 Postmarket Experience

Orexigen submitted an analysis of the data contained in the FDA AERS (Adverse Event Reporting System) database in order to have an understanding of the safety profiles for bupropion and naltrexone based on the AEs reports that have been submitted to the FDA.

- Across bupropion products, the events returned with a high frequency and noted to be most common were the following, (all of which are present in the bupropion prescribing information): depression, insomnia, anxiety, irritability, aggression, confusional state, suicidal ideation, suicide attempt and intentional overdose within the Psychiatric Disorders SOC, convulsion from the Nervous System Disorders SOC and rash and urticaria from Skin and Subcutaneous Tissue Disorders SOC. Several of the most common listed events in the prescribing information reported for bupropion were noted to meet potential signal criteria, including: depression, irritability, aggression, suicidal ideation and suicide attempt, from the Psychiatric Disorders SOC and convulsion-related events from the Nervous System Disorders SOC. Poisoning deliberate and tobacco use and tobacco user from the Injury Poisoning and Social SOCs, respectively, also met potential signal criteria.

- For naltrexone products, the events returned with a high frequency and noted to be most common were the following listed events: vomiting from the Gastrointestinal Disorders SOC, drug interaction from the General Disorders SOC, drug withdrawal syndrome from the Social Circumstances SOC, and nervousness and depression from the Psychiatric Disorders SOCs. Several of the most common listed events reported for naltrexone were noted to meet potential signal criteria, including: drug interaction from the General Disorders SOC, and drug withdrawal from the Social Circumstances SOC. However, several unlisted events that were not reported with the highest frequency met the criteria for potential safety signals, including alcohol withdrawal syndrome, alcoholism, and drug dependence from the Psychiatric Disorders SOC and alcohol poisoning from the Injury, Poisoning and Procedural Complications SOC.

In the 4-month safety update, the sponsor updated their analysis of the postmarketing data through reviews of the data retrieved from the AERS database through the 3rd quarter of 2009. The update confirmed that the key safety signals remain the risk of suicidality with antidepressants, seizures with bupropion, and issues related to the use of naltrexone with opiates.

DMEP asked the Office of Surveillance and Epidemiology (OSE) to provide an analysis of AERS reports associated with bupropion (Wellbutrin, Zyban, Aplenzin) and naltrexone (Revia, Vivitrol). This analysis[50] focused on reports describing concurrent use of bupropion and naltrexone, but also provided an overview of the U.S. serious reports associated with bupropion and naltrexone as single agents. Safety concerns with bupropion center around the 1) dose-related noradrenergic and dopaminergic effects that are primarily neuropsychiatric (seizures, suicidality, mood changes) and cardiovascular, and 2) idiosyncratic reactions such as allergic reactions and liver injury.

Bupropion Reports in AERS
Serious adverse events associated with bupropion that are frequently reported to AERS are consistent with those described in the bupropion labeling. Of note, between marketing and January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use), the top ten most frequently reported events are Convulsions, Urticaria, Grand Mal Convulsions, Dermatitis, Pruritus, Dyspnea, Tremor, Dizziness, Overdose (intentional and unintentional), and Drug Interaction.

Bupropion Deaths
AERS contains 166 reports of death associated with bupropion that were reported to FDA between the initial marketing approval in 1985 and January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use). The three most frequently reported events associated with a bupropion death are Intentional Overdose or Suicide (80 reports), Cardiac Arrhythmia (18 reports), and Seizure (14 reports).

Naltrexone Reports in AERS

50 Wyeth J. AERS Review for NDA 200063 Bupropion/Naltrexone (Contrave) 17 Aug 2010

Serious adverse events associated with naltrexone that are frequently reported to AERS are consistent with the naltrexone labeling. Of note, the top ten most frequently reported events are Vomiting, Nausea, Diarrhea, Death, Injection Site Pain, Depression, Drug Ineffective, Drug Withdrawal Syndrome, Condition Aggravated, and Drug Interaction.

Naltrexone Deaths
Since marketing through January 1, 2010, AERS contains 52 naltrexone reports associated with death. The three most frequently reported events associated with a naltrexone death are Suicide, Overdose (unclear if intentional or accidental), and Rapid or Ultra Rapid Detoxification.

AERS Review of Concurrent Use of Bupropion and Naltrexone
In July 2010, OSE performed an analysis of AERS cases associated with concurrent use of bupropion and naltrexone and 24 cases (US: 21, Foreign: 3) were identified between 1996 and 2010. Seventeen of the twenty-four cases reported bupropion and/or naltrexone as a suspect drug in causing the adverse event, and seven cases reported bupropion and naltrexone as concomitant drugs. No deaths were reported. None of the cases suggested bupropion and or naltrexone were prescribed for weight management. None of the cases implicated both bupropion and naltrexone as suspect in having caused the adverse event. However, attribution was difficult because of the concomitant use of multiple medications, and presence of underlying drug and or alcohol abuse.

8 Appendices

APPENDIX A More Detailed Information on Inclusion/Exclusion Criteria

Inclusion Criteria Common to the Four Phase 3 Trials (NB-301, NB-302, NB-303, NB-304)

- Free of opioid medication for 7 days prior to randomization
- No clinically significant abnormality of serum albumin, blood urea nitrogen, bilirubin, calcium and phosphorus, hematocrit, white blood cell count, white cell differential, or platelets or on urinalysis
- ALT and AST levels within 2.5 x upper limit of normal (ULN)
- If woman of child-bearing potential, must be non-lactating and agree to use effective contraception throughout the study period and 30 days after discontinuation of study drug and must have a negative serum pregnancy test
- Inventory of Depressive Symptomatology Subject-Rated (IDS-SR) scores <2 on items 5 (sadness), 6 (irritability), 7 (anxiety/tension) and 18 (suicidality), and IDS-SR total score is <30.

Inclusion Criteria Unique to Specific Trials
Inclusion Criteria Unique to NB-301, NB-302, NB-303

- Have body mass index (BMI) ≥30 and ≤45kg/m^2 for subjects with uncomplicated obesity, and BMI of ≥27 and ≤45kg/m^2 for subjects with obesity and controlled hypertension and/or dyslipidemia

- Normotensive (systolic ≤140 mm Hg; diastolic ≤90 mm Hg). Anti-hypertensive medications are allowed with the exception of alpha-adrenergic blockers, and clonidine. Medical regimen must be stable for at least 6 weeks prior to randomization (NB-301, NB-303). Medical regimen must be stable for at least 8 weeks (NB-302).

Inclusion Criteria Unique to NB-301, NB-303, NB-304

- TSH within normal limits or normal triiodothyronine (T3), if TSH is below normal limits
- Negative urine drug screen

Inclusion Criteria Unique to NB-302

- Non-smoker and no use of tobacco or nicotine products for at least 6 months prior to screening
- LDL cholesterol <190 mg/dL and triglycerides <400 mg/dL. Medications for treatment of dyslipidemia are allowed as long as medical regimen has been stable for at least 8 weeks
- Fasting glucose ≤126 mg/dL on no hypoglycemic agents
- TSH within 1.5 x ULN or normal T3, if TSH is below normal limits
- Completed food diary for 6 out of 7 consecutive days during screening period

Inclusion Criteria Unique to NB-301 and NB-303

- Fasting glucose <126 mg/dL on no hypoglycemic agents, fasting triglycerides <400 mg/dL
- Medications for treatment of dyslipidemia are allowed as long as medical regimen has been stable for at least 6 weeks prior to randomization

Inclusion Criteria Unique to NB-304

- Body mass index (BMI) ≥27 and ≤45 kg/m^2
- Diagnosed with type 2 diabetes mellitus and on no injectable antidiabetes medication or inhaled insulin for more than 3 months prior to randomization
- On oral single or combination hypoglycemic medications (biguanides, thiazolidinediones, meglitinides, α-glucosidase inhibitors, sulfonylureas, DPP4 inhibitors) or no medications for the treatment of Type 2 Diabetes Mellitus. Oral hypoglycemic medication must be stable for at least 3 months prior to randomization.
- Systolic blood pressure <145 mm Hg; diastolic blood pressure <95 mm Hg. Antihypertensive medications are allowed with the exception of alpha-adrenergic blockers and clonidine. Antihypertensive treatment regimen must be stable for at least 4 weeks prior to randomization.
- Medications for treatment of dyslipidemia are allowed with the exception of cholestyramine and cholestipol as long as medical regimen has been stable for at least 4 weeks prior to randomization
- HbA1c between 7% and 10%, fasting blood glucose <270 mg/ml, fasting triglycerides <400 mg/dL
- Creatinine levels must be ≤1.4 mg/dL for women, ≤1.5 mg/dL for men

Exclusion Criteria Common to the Four Phase 3 Trials (NB-301, NB-302, NB-303, NB-304)

- Serious medical conditions (including but not limited to ongoing renal or hepatic insufficiency, Class III or IV congestive heart failure; history of myocardial infarction, angina pectoris, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke
- History of malignancy with exception of non-melanoma skin cancer or surgically cured cervical cancer within the previous 5 years
- Serious psychiatric illness, including lifetime history of bipolar disorder, schizophrenia or other psychosis, bulimia, and anorexia nervosa; current serious personality disorder, (e.g., borderline or antisocial), current severe major depressive disorder, recent (previous 6 months) suicide attempt or current active suicidal ideation, recent hospitalization due to psychiatric illness
- A response to Bipolar Disorder questions indicating the presence of Bipolar Disorder
- In need of medications for the treatment of a psychiatric disorder (with the exception of short-term insomnia) within the previous 6 months
- History of drug or alcohol abuse or dependence within 1 year
- Screening or Baseline ECG with a QTc interval (Bazett's formula) >450 msec (men) or >470 msec (women) or the presence of any clinically significant cardiac abnormalities, including but not limited to patterns consistent with recent myocardial ischemia, electrolyte abnormalities, atrial or ventricular dysrhythmia or significant conduction abnormalities
- History of surgical or device (e.g., gastric banding) intervention for obesity
- History of seizures of any etiology, or of predisposition to seizures (e.g., history of cerebrovascular accident, head trauma with >5 minutes loss of consciousness, concussion symptoms lasting >15 minutes, brain surgery, skull fracture, subdural hematoma, or febrile seizures)
- History of treatment with bupropion or naltrexone within the preceding 12 months
- History of hypersensitivity or intolerance to bupropion or naltrexone
- Participation in a weight loss management program within one month prior to randomization
- Pregnant or breast-feeding women or planning to become pregnant during the study period or within 30 days of discontinuing study drug
- Planned surgical procedure that can impact the conduct of the study
- Use of investigational drug, device or procedure within previous 30 days
- Participation in any previous clinical trial sponsored by Orexigen Therapeutics
- Any condition which in the opinion of the investigator makes the subject unsuitable for inclusion in this study

Exclusion Criteria Unique to Specific Trials

Exclusion Criteria Unique to NB-301, NB-302, and NB-303

- Type I or Type II diabetes mellitus
- Obesity of known endocrine origin (e.g., untreated hypothyroidism, Cushing's syndrome, established Polycystic Ovary Syndrome)
- Loss or gain of more than 4.0 kg within 3 months prior to randomization

- Use of drugs, herbs, or dietary supplements believed to significantly affect body weight within one month prior to randomization

Exclusion Criteria Unique to NB-301, NB-303, NB-304

- Excluded concomitant medications: any psychotropic agents (including antipsychotic, antidepressant, anxiolytic, mood stabilizer, anticonvulsant agents or agents for the treatment of Attention Deficit Disorder) with the exception of low dose benzodiazepine or hypnotic agents for the treatment of insomnia (up to 2 mg lorazepam/day or equivalent dose of a benzodiazepine or hypnotic agent); any anorectic or weight loss agents; any over-the-counter dietary supplements or herbs with psychoactive, appetite or weight effects; alpha-adrenergic blockers; dopamine agonists; clonidine; coumadin; theophylline; cimetidine; oral corticosteroids; cholestyramine, cholestipol, DepoProvera®; smoking cessation agents; use of opioid or opioid-like medications, including analgesics and antitussives
- Change in smoking status or in tobacco or nicotine use in the previous 3 months or planned during study participation

Exclusion Criteria Unique to NB-302

- Excluded concomitant medications: any psychotropic agents (including antipsychotic, antidepressant, anxiolytic, mood stabilizer or anticonvulsant agents) with the exception of low dose benzodiazepine or hypnotic agents for the treatment of insomnia; any psychotropic agents

Exclusion Criteria Unique to NB-304

- Type I Diabetes Mellitus
- Subjects with "brittle-diabetes" or any hospitalization or emergency room visit due to poor diabetic control within the past 6 months, previous history of diabetes-related dehydration leading to hospitalization, history or evidence of ketoacidosis
- Obesity of known endocrine origin other than Diabetes Mellitus (e.g., untreated hypothyroidism, Cushing's syndrome, established Polycystic Ovary Syndrome)
- Diabetes Mellitus secondary to pancreatitis or pancreatectomy
- Loss or gain of more than 5.0 kg within previous 3 months
- Severe microvascular or macrovascular complications of diabetes, including but not limited to proliferative retinopathy, active limb ulcerations, amputations of metatarsals or above

Non-drug Ancillary Therapy for Weight Loss Among the 4 Phase 3 Trials

- Trials NB-301 and NB-303: All subjects received ancillary therapy at baseline and Weeks 12, 24, 36 and 48. Subjects were instructed to follow a hypocaloric diet representing a deficit of 500 kcal per day based on the World Health Organization (WHO) algorithm for calculating resting metabolic rate. Adjusted body weight was used to calculate energy needs because subjects were 120% greater than ideal body weight. Subjects received written instructions on behavioral modification techniques. Subjects were encouraged to increase physical activity, with a prescription for walking starting with at least 10 minutes on most days of the week and increasing this gradually to 30

minutes on most days of the week throughout the study. They were encouraged to lose weight and maintain weight loss, and were encouraged to follow the prescribed program. Participation in any other weight loss program was not permitted. The use of meal replacements (such as SlimFast® or Weight Watchers®) was discouraged but occasional use did not necessitate withdrawal from the study.

- Trial NB-304 (subjects with Type 2 DM): All subjects received ancillary weight loss therapy at baseline and Weeks 4, 16, 28, and 40. Ancillary therapy consisted of diet instruction, behavior modification advice, and physical activity suggestions. Subjects were instructed to follow a hypocaloric diet representing a deficit of 500 kcal/day based on the World Health Organization's (WHO) algorithm for calculating resting metabolic rate. Adjusted body weight was used to calculate energy needs because subjects were 120% greater than ideal body weight. Subjects received behavioral modification advice, including written instructions. Dietary counseling was conducted in accordance with the American Diabetes Association and American Dietetic Association guidelines for counseling diabetics. "Exchange Lists for Weight Management, 2nd edition" booklets were provided to trial participants to facilitate adherence to prescribed dietary regime. Subjects were encouraged to increase physical activity, with a prescription for walking at least 30 minutes three times per week. Subjects were encouraged to follow the prescribed program. Participation in any other organized weight loss program was not permitted. The use of meal replacements (such as Slim Fast® or Weight Watchers®) were discouraged, but occasional use despite contrary instructions did not necessitate withdrawal from the study.
- Trial NB-302: Intensive Behavior Modification Program: All subjects were to participate in an intensive behavior modification program that included three components: dietary instruction, closed group sessions, and prescribed exercise. Dietary instructions were provided at baseline (Day 1). Subjects were requested to maintain daily food diaries. Subjects began closed group sessions no later than 4 weeks after randomization. Closed group sessions (10 to 20 subjects per session) were 90 minutes in duration (included weigh-in) and occurred once every week for 16 weeks, once every 2 weeks for 12 weeks, and monthly thereafter, for up to 28 sessions. Subjects who prematurely discontinued study drug were encouraged to continue participation in the intensive behavior modification program and to return to the study center for a body weight measurement (every 4 weeks) and waist circumference measurement (Weeks 28 and 56).

APPENDIX B Routine Clinical Testing

NB-301, -302, -303, and -304
Hematology: red blood cell (RBC) count, WBC count with differential, hemoglobin, hematocrit, and platelet count. Hematology tests were performed at screening, Weeks 4, 16, 28, 40 and 56 (or early termination).

NB-301, -302, and -303
Chemistry: Screening (fasting): albumin, ALT, AST, bilirubin (direct/indirect), blood urea nitrogen (BUN), calcium, creatinine, glucose, sodium, potassium, chloride, phosphorus, and uric acid. **Baseline (fasting):** ALT, AST, bilirubin (direct/indirect), BUN, creatinine, and glucose. **Weeks 4, 16, and 40 (nonfasting):** ALT, AST, bilirubin (direct/indirect), BUN, and creatinine. **Weeks 28 and 56 (fasting):** albumin, ALT, AST, bilirubin (direct/indirect), BUN, calcium, creatinine, glucose, sodium, potassium, chloride, phosphorus.

NB-304
Chemistry (fasting): Blood samples to determine ALT, AST, bilirubin (direct/indirect), BUN, and creatinine concentrations were collected at screening, baseline (Day 1), and Weeks 4, 16, 28, 40, and 56 (or early termination). Blood samples to determine albumin, calcium, and phosphorus concentrations were collected at screening and Weeks 28 and 56 (or early termination).

NB-301, -302, and -303
Lipids (fasting): total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Blood samples for fasting lipids were obtained at screening, baseline, Weeks 28 and 56.

NB-301 only
hs-CRP: Blood samples for hs-CRP were obtained at baseline and at Weeks 28 and 56. This analyte was evaluated as an obesity-associated cardiovascular risk factor.

NB-301, -302, and -303
Insulin (fasting): Blood samples for fasting insulin were obtained at baseline and at Weeks 28 and 56. This analyte was evaluated as an obesity-associated cardiovascular risk factor.

NB-301 only
HOMA-IR: derived using fasting blood glucose and fasting plasma insulin levels, calculated for Weeks 28 and 56.

NB-301, -302, -303, and -304
Urinalysis: appearance, specific gravity, pH; dipstick for protein, blood, glucose, and ketones; microscopic examination of sediment. A urine drug screen was performed for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, methaqualone, methadone, opiates, phencyclidine, and propoxyphene. A urine sample for urinalysis testing was collected at screening and Week 56, or at the investigator's discretion at other visits for drug screening.

NB-301, -302, -303, and -304
Serum Pregnancy: For all female subjects, a serum pregnancy test was performed at screening and Week 56 (or early termination).

NB-301, -302, and -303
Thyroid-stimulating Hormone: Test was performed at screening only as part of the inclusion criteria.

All clinical laboratory tests were analyzed by a central laboratory (Quintiles Laboratories, Worldwide).

The following refer to NB-301, -302, -303, and -304

Vital Sign Measurements Including Height

Systolic and diastolic blood pressure and pulse rate measurements were recorded by study personnel at every study visit. To minimize the effects of blood pressure and pulse rate variability, three blood pressure and pulse readings were obtained after the subject had been sitting for at least 5 minutes and an average of these was calculated. Height was measured (without shoes) at screening only.

Electrocardiograms

A standard 12-lead ECG was performed at screening, and Weeks 4, 24, and 56 (or early termination) and read by the investigators at the study centers. The ECG parameters included ventricular rate, PR interval, QRS duration, QT interval, QTcB, and QT interval corrected by the method of Fridericia (QTcF). Clinical assessment of a QTc-related AE was based on QTcB. Any clinically significant ECG changes from baseline/screening were recorded on the AE electronic case report form (eCRF).

Physical Examinations Including Neurologic Examinations

Physical examinations were performed at screening and Week 56 (or early termination). A neurologic examination was performed at Screening and at Weeks 4, 28 and 56. The neurological examination included mental status, cranial nerves, motor examination, reflex examination, cerebellar function, and sensory examination.

APPENDIX C Select Patient Narratives

1) *Post-treatment Serious Adverse Events: Acute Myocardial Infarction*

- Subject 086-NB-301-040: a 50-year-old White male randomized to receive naltrexone SR 16 mg/bupropion SR 360 mg. The subject had a relevant medical history of active reflexes abnormal, arthritis, gastroesophageal reflux disease, erectile dysfunction, headache, hyperglycemia, hyperlipidemia, back pain, hypertension, inactive musculoskeletal chest pain, sciatica, pneumothorax, and tendonitis. The subject was receiving the following concurrent medications: acetylsalicylic acid, atorvastatin calcium, fenofibrate, fish oil, and ranitidine hydrochloride. At baseline (Day 1) the subject's pulse rate and blood pressure were 69 beats per minute and 115/77 mm Hg, respectively. The last recorded heart rate and blood pressure at the subject's Early Termination visit (Day 29) was 63 beats per minute and 112/73 mm Hg—however the subject had stopped NB16 on Day 13. On Day 8, the subject experienced gastroesophageal reflux disease and nausea. The subject discontinued study drug for the primary reason of gastroesophageal reflux disease and the secondary reason of nausea. The last confirmed dose of study drug was received on Day 13. The last study visit occurred on Day 29. On Day 49, the subject experienced acute myocardial infarction. The subject presented to the emergency room on Day 49 with complaints of chest pain that started the previous evening (Day 48) and persisted throughout the day on Day 49 at a milder level. The subject's troponin was found to be elevated (value not specified) and the ECG noted sinus rhythm with nonspecific ST-T changes which was interpreted

as borderline ST segment depressions laterally. The subject underwent cardiac catherization and a stent was placed in the right coronary artery. Approximately 20% stenosis was observed in the proximal segment of the left anterior descending artery just after the first septal branch. Mild coronary artery disease of the left anterior descending artery was noted. Approximately 40% stenosis was observed in the left anterior descending artery, but the main left anterior descending artery was free of disease to the apex. The right coronary artery was totally occluded in the proximal segment.

2) *Atherosclerotic Disease*

- *Subject 065-NB-303-048*: 50-year-old White female randomized to receive naltrexone SR 32mg/bupropion SR 360 mg. The subject reported the following relevant medical history: active coronary artery disease, angina pectoris, anxiety, seborrhoeic dermatitis, hyperlipidemia, hypertension, and hypertriglyceridemia. The subject was receiving the following concurrent medications: acetylsalicylic acid, ketoconazole, and lisinopril. At baseline, the subject was a current user of tobacco. The subject had a baseline heart rate and blood pressure of 87 beats per minute and 119/79 mg Hg, respectively. Both the subject's screening and Week 4 (Day 29) ECGs were normal. On Day 85, the subject experienced myocardial infarction (verbatim: myocardial infarction). On that day, the subject came to the study site for the Week 12 visit and reported heartburn for the past three days with increasing frequency and discomfort. Her blood pressure and pulse were 127/80 mm/Hg and 90 beats per minute, respectively. The chest discomfort, which was substernal and epigastric, had become quite painful and she had began experiencing the burning sensation nearly every hour. The subject was referred to her physician who performed an ECG. The ECG revealed terminal T wave inversions in the precordial leads. The subject was sent to the emergency room where she had more diffuse and marked terminal precordial T wave inversions as well as a troponin level of 0.8 (mildly elevated)(reference range/units not provided). The subject was admitted to the hospital with acute myocardial infarction for cardiac catheterization. She was found to have stenosis of the left anterior descending coronary artery, described as a small size vessel with mild diffuse luminal irregularity and a focal 99% occlusion in the mid segment with slow flow distally. The left anterior descending artery was revascularized with an Endeavor drug eluting stent. The subject was treated with enoxaparin (Day 85), glyceryl trinitrate (Days 85-86), clopidogrel (Days 85-ongoing) and metoprolol succinate (Days 85-ongoing). The subject was discharged from the hospital on Day 86. The event myocardial infarction resolved on Day 85 and the event coronary artery disease was ongoing. On Day 86, shortly after discharge, the subject experienced a complication from the cardiac catheterization which resolved on Day 139. She was found to have 80% stenosis of the femoral artery and successfully underwent an endarterectomy on Day 139. The subject did not complete drug treatment due to the primary reason of myocardial infarction and date of last confirmed dose of study drug is Day 85.

- *Subject 060-NB-304-016:* A 44-year-old White male was randomized in Trial NB-304 for obese subjects with Type 2 Diabetes Mellitus to receive naltrexone SR 32 mg/bupropion SR 360 mg. The subject had a relevant medical history of active drug hypersensitivity and hyperlipidemia, and inactive asthma and tendon rupture, and was receiving the following concurrent medications: glipizide, metformin, pioglitazone, pravastatin, and fenofibrate. The subject quit smoking about two and a half years ago. The subject had a normal screening ECG. Day 1 blood pressure was 112/77 mm Hg and the pulse was 77 beats per minute. At the subject's Week 8 visit on Day 52, the blood pressure was 101/61 mm Hg and the pulse was 76 beats per minute. On Day 55, the subject experienced dizziness, nausea, and hyperhidrosis. These events resolved on Day 56. On Day 56, the subject experienced axillary pain and a myocardial infarction (verbatim: myocardial

infarction). The subject had experienced left axillary pain radiating down the left arm for the prior two days. He went to his primary care physician on Day 57 who performed an ECG which revealed mild ST- elevation in leads 2-3 and AVF. The subject was referred to the emergency department where an ECG revealed normal sinus rhythm, mild ST segment elevation in lead 3 only and mild ST segment depression in leads V2 to V6; these were new changes from prior ECGs. The diagnosis was a non ST elevation myocardial infarction with ongoing electrocardiogram changes and the subject was admitted on Day 57. It was felt that the myocardial infarction most likely occurred within the last two days from admission. In the emergency room, the subject's blood pressure was 119/79 mm Hg and the pulse was 79 beats per minute. Per the hospital records, the subject was started on Lovenox and sublingual nitroglycerin. On Day 57 at 1236 hours, the CPK was 733 U/L (reference range: 33 – 170 U/L), CK-MB was 103.3 ng/mL (reference range: 0.0 – 4.0 ng/mL), the CK-MB index was 14.1 % (reference range: < 2.5 %), and troponin I was 15.58 ng/mL (reference range: < 0.06 ng/mL). These results were consistent with acute coronary syndrome. On Day 57 at 2035 hours, CPK was 651 U/L, CK-MB was 63.8 ng/mL, and the CKMB index was 9.8 %. On Day 58, the CPK was 560 U/L, and troponin I was 26.35 ng/mL. The INR was 0.95 (reference range for acute myocardial infarction: 2.0 – 3.0). A chest X-ray was within normal limits. The subject was admitted for an urgent cardiac catheterization, ventriculogram, and coronary angiogram, and underwent a percutaneous coronary intervention of the distal right coronary artery near the crux, which was 100% occluded with a large thrombus. On Day 58, the subject had an echocardiogram and doppler; it showed a mildly dilated left ventricle, mildly decreased left ventricular function, an estimated left ventricular ejection fraction of 45 – 50 %, and that the left ventricular inferior was severely hypokinetic. The event of myocardial infarction was treated with acetylsalicylic acid, carvedilol, lisinopril, and clopidogrel from Days 57 - ongoing. The myocardial infarction and axillary pain both were considered to be resolved on Day 57. The subject was discharged from the hospital on Day 59. The subject did not complete study for the primary reason of myocardial infarction. The date of last confirmed dose is Day 57. The subject had an early termination visit on Day 70.

- *Subject 075-NB-304-017:* A 62-year-old White female, was randomized in Trial NB-304 for obese subjects with Type 2 Diabetes Mellitus to receive placebo. The subject had a relevant medical history of active anemia, arthritis, hot flush, hypercholesterolemia, migraine, and seasonal allergy, and was receiving the following concurrent medications: chlorphenamine maleate, hydroxyzine, ibuprofen, lisinopril, lovastatin, nicotinic acid, lipitac, and glipizide. Per the hospital report, the subject also has a history of hypertension that was not captured in the subject's medical history for this study. On Day 90, the subject experienced a cerebrovascular accident (verbatim: stroke). The subject went to the emergency room complaining of a coordination deficit, weakness in the left leg, and difficulty walking. In the emergency room, blood pressure was 141/82 mm Hg and the pulse was 81 beats per minute. The subject was alert and oriented x 4, and cranial nerves II to XII intact, with the exception of VII, with a subsequent left facial droop. The subject had a left sided upper and lower extremity power of 3/5 and deep tendon reflexes were decreased on the left side. The right side was unremarkable and gait was not tested. A chest x-ray and EKG were normal. The laboratory tests were unremarkable, with the exception of a BUN of 24 mg/dL (reference range: 9 – 20 mg/dL). The head CT showed no bleed or acute changes. The event was treated with acetylsalicylic acid from Day 90 – ongoing, and the subject was admitted to the stroke unit. A subsequent MRI revealed a focal ischemic injury of the right insula. An MRA of the head and neck was normal. The left lower extremity weakness improved. The subject had no speech or swallowing deficits. The subject was discharged on Day 92 with instructions to follow up with the neurology clinic. The cerebrovascular accident was resolved on Day 90. The subject did discontinue study drug due to this event, and the date of the

last confirmed dose of study drug is Day 89. The subject discontinued from the study assessments on Day 296 for the same reason.

3) *Seizure and Convulsions*

- Subject **066-NB-303-016**, a 40-year-old White female, was randomized to receive naltrexone SR 32 mg/bupropion SR 360 mg with fast titration. She had no prior history of convulsion or seizure disorder. The subject reported the following relevant medical history: active rhinitis allergic, gastroesophageal reflux disease, insomnia, hemorrhoids, irritable bowel syndrome, restless leg syndrome, and inactive depression and cyst. At the time of the event, the subject was receiving eugynon and polycarbophil calcium. On Day 144, the subject had a witnessed seizure during which she had shaking of her head, rolling of the eyes backwards, and foaming at the mouth with associated unresponsiveness. When EMS arrived, the subject was awake but confused. Initial laboratory tests, head CT, MRI of the brain, MRA of the head and neck, 2D echocardiogram, and ECG were unremarkable. A neurology consult was requested and a subsequent EEG was suggestive of a partial seizure disorder arising from the left temporal lobe. The subject was stable without further seizure and no anti-epileptic medication was initiated; paracetamol was the only medication taken that day. The last dose of study drug was taken on Day 144. The remainder of the hospital course was uneventful and the subject was discharged home in stable condition on Day 147. A subsequent EEG on Day 175 showed no focal or epileptiform features and was less abnormal compared to the previous EEG, but showed the presence of low voltage fast activity most consistent with medication effect, sedative, hypnotics, anti-anxiety medications, etc. At the early termination visit, the subject reported having an episode of presyncope (Days 148-193) and syncope (Days 150-159). These events were unwitnessed. The subject was treated for the event of presyncope with clonazepam (Days 177-193).The subject was seen by a neurologist on Day 191 who recommended no anti-seizure medication and follow up in 3 months. The subject did not complete study drug due to the event of convulsion and discontinued from the study on Day 195. The subject subsequently reported that there were no more seizures since the original one reported. In addition, the subject was found to have an abnormal mammogram on Day 149 ((b) (6)). Biopsy on Day 188 (b) (6) revealed invasive lobular carcinoma. The subject also underwent a lumpectomy, followed up with chemotherapy that started in (b) (6) and ended in (b) (6).

- Subject **122-NB-304-014**, a 59-year-old White female in the NB32 group, had a relevant medical history of Type 2 diabetes and hyperlipidemia. Relevant concomitant medications were atorvastatin calcium, lisinopril, glibenclamide, metformin, and rosiglitazone. The subject had one prior AE of hypoglycemia on Day 38. On Day 110, while shopping, the subject's daughter noticed that the subject was pale. The daughter thought the subject was hypoglycemic and gave the subject chocolate. The subject fell and was described as having convulsive activity, bit her tongue, was incontinent of urine and stool and turned blue. By the time EMS arrived the episode had stopped. The subject regained consciousness about 7 to 10 minutes later with no recollection of the episode. EMS tested the subject's blood sugar which was initially 74 and subsequently rose to 85 and then to the 90s on two other checks. Per the subject, the seizure was preceded by two hot flashes and a feeling of lightheadedness. Per the subject's husband, the subject stopped breathing during the seizure and CPR was performed. Neurological examination was normal. The subject was admitted to the hospital on Day 110 for evaluation and given IV dilantin and levetiracetam on Day 110. During admission, no arrhythmias on telemetry were noted and a myocardial infarction was ruled out. A CT scan, MRI, and EEG were normal. The subject was discharged on Day 112 on no seizure medication and was advised not to drive for 6 months. Per the neurologist, it was thought that the event was an isolated seizure in context of probable

hypoglycemia. It was difficult to determine if the blood sugar level was sufficiently low enough to cause seizure; the subject had candy in her mouth and blood sugar measurements increased over three consecutive measurements. Study drug was discontinued while in the hospital and then restarted. Study drug was stopped permanently after the last dose on Day 119. No additional events of grand mal convulsion were reported. The subject discontinued the study on Day 141 due to a grand mal convulsion. A follow up neurological and physical exam were both normal. Per follow up neurological exam, the subject has remained seizure free for a total of 6 months, even though her blood glucose has dropped into the 30s on occasion. As a result, the subject's endocrinologist has lowered the glyburide dose.

4) *Syncope*

Some of the narratives from subjects that experienced syncope are provided below:

- NB16 Subject 079-NB-301-033: A 40 year-old female with a medical history of hypertriglyceridemia and low HDL was randomized to receive bupropion 360 mg and naltrexone 16 mg in Trial NB-301. On Day 183, the subject experienced a loss of consciousness (mild, possibly related, resolved the same day). No blood pressure reading or heart rate was reported (most recent blood pressure prior to the event was 115/72 mm Hg and heart rate of 93 bpm on Day 166). Electrocardiogram results were found within normal limits while hematology and chemistry results found out of normal range were not relevant to event of syncope. Concomitant medication included lansoprazole (1997- continuing). Abnormal muscle activity of tremor (mild, possibly related, resolved Day 34) was reported on Day 29. Study drug was not changed and the subject completed the study.
- NB32 Subject 042-NB-303-013- reported a TEAE of syncope which led to study drug discontinuation. The subject is a 36-year-old White female randomized to receive naltrexone SR 32 mg/bupropion SR 360 mg with fast titration. The subject reported the following relevant medical history: HDL-C decreased and upper respiratory tract infection. At the time of the event, the subject was receiving the following concurrent medications: fish oil, multivitamin, and estrogens. On Day 34, the subject experienced syncope (verbatim: syncope episode), which resolved on Day 34. On Day 34, the subject was moving a heavy piece of equipment at work when she cried out and fell to the floor. A coworker stated that her arms and legs were shaking and she was foaming at the mouth. The subject was transported by EMS to the ER where she was diagnosed with syncope episode due to valsalva maneuver. The subject saw a neurologist who requested that she stop study drug. Subject discontinued from study drug on Day 48 due to adverse event.
- NB32 Subject 075-NB-303-022: a 43 year-old female with a relevant medical history of fibromyalgia and dyslipidemia was randomized to receive slow titration of bupropion 360 mg and naltrexone 32 mg. On Day 18, the subject experienced dizziness (mild, unlikely related-continuing). On Day 55, the subject experienced syncope (mild, unlikely related, resolved the same day). No blood pressure reading or heart rate was reported (most recent blood pressure prior to the event was 103/61 mm Hg and heart rate of 62 bpm on Day 31). Electrocardiogram, hematology, and chemistry results were found within normal limits. Concomitant medication was not reported. No TEAE of abnormal muscle activity was reported. Study drug was not changed and the subject terminated the study early (lost to follow-up).
- NB32 Subject 119-NB-303-017- reported a TEAE of syncope which led to study drug discontinuation. She is a 34-year-old White female randomized to receive naltrexone SR 32 mg/bupropion SR 360 mg with fast titration. The subject was subsequently re-randomized to receive naltrexone SR 48 mg/bupropion SR 360 mg. The subject reported the following medical history: breast cosmetic surgery, hypercholesterolemia, tubal ligation, and inactive anxiety, congenital anomaly, depression, irritable bowel syndrome, migraine, nephrolithiasis, sinusitis,

strabismus, and vertigo. At the time of the event, the subject was taking the following concurrent medications: multivitamin and drospirenone with ethinylestradiol. On Day 222, the subject experienced syncope (verbatim: syncope), which resolved on Day 222. The investigator judged this event not serious, moderate, and related to study drug. Other adverse events that contributed to discontinuation included dizziness (Day 198 – Day 223), headache (Day 198 - Day 223), insomnia (Day 198 - Day 223), contusion (Day 222 - ongoing), nausea (Day 222). Other adverse events reported by the subject included dizziness (Day 11 - Day 23), nausea (Day 11 - Day 23), viral infection (Day 44 - Day 51), headache (Day 78 - Day 78), headache (Day 99- Day 100), ovarian cyst (Day 152 - ongoing). Subject discontinued from study drug on Day 222 due to adverse event.

APPENDIX D Special Safety Topic Preferred Terms

(only terms present in the database were included)

1) The Cardiovascular special topic consisted of the following subtopics, categories, and preferred terms:

Subtopic	Category	Preferred Terms
Atherosclerotic Disease	Major CV	Myocardial infarction, cerebrovascular accident
	Angina	Angina pectoris, angiopathy, coronary artery disease, coronary artery occlusion, troponin increased
	Potential CV symptoms	Palpitations, chest pain, chest discomfort, oedema peripheral, cardiac murmur, oedema, cardiovascular disorder, cyanosis, exercise tolerance decreased, generalised oedema, gravitational oedema
	ECG changes	Heart rate increased, electrocardiogram abnormal, electrocardiogram PR shortened, electrocardiogram ST segment depression, electrocardiogram ST-T segment abnormal, electrocardiogram T wave abnormal, heart rate decreased, left atrial dilatation, QRS axis abnormal
	Potential stroke symptoms	Muscular weakness, altered state of consciousness, dysarthria, expressive language disorder, facial palsy, loss of consciousness, positive Rombergism
Arrhythmias	Arrhythmias, atrial	Sinus bradycardia, atrial fibrillation, supraventricular tachycardia, atrial flutter, bradycardia, sinus tachycardia, arrhythmia supraventricular
	Arrhythmias, other	Tachycardia, extrasystoles, ventricular extrasystoles, arrhythmia, heart rate irregular
	Repolarization abnormalities	Electrocardiogram QT prolonged

	Conduction disorders	Atrioventricular block first degree, bundle branch block right, atrioventricular block, bundle branch block left, bundle branch block
Congestive Heart Failure	Congestive heart failure	Cardiac failure, ejection fraction decreased
	Potential CHF symptoms	Dyspnoea, dyspnoea exertional, pulmonary congestion, cardiomegaly, pericardial effusion

2) The Psychiatric special topic consisted of the following subtopics, categories, and preferred terms:

Subtopic	**Category**	**Preferred Terms**
Anxiety	Anxiety	Anxiety, nervousness, tension, panic attack, fear, panic reaction, hyperventilation, generalised anxiety disorder
	Potential anxiety symptoms	Stress, restlessness, acute stress disorder, social avoidant behaviour, hypervigilance, social phobia
Depression	Depression	Depression, depressed mood, dysthymic disorder, major depression, suicidal ideation
	Potential depression symptoms	Irritability, middle insomnia, libido decreased, stress, poor quality sleep, tearfulness, psychomotor hyperactivity, apathy, crying, depressive symptom, anhedonia, bereavement reaction, emotional distress, loss of libido, negative thoughts
Sleep Disorders	Sleep disorders	Insomnia, sleep disorder, abnormal dreams, middle insomnia, poor quality sleep, initial insomnia, nightmare, sleep apnoea syndrome, terminal insomnia
	Somnolence	Somnolence, sedation, hypersomnia
Hostility	Aggression	Irritability, affect lability, agitation, psychomotor hyperactivity, anger, aggression
Mood Disorders	Mood disturbance	Affect lability, mood altered, mood swings, euphoric mood, elevated mood, premenstrual syndrome, tachyphrenia,
	Potential mood disorders	Anger, crying, flat affect
Psychosis	Potential psychosis symptoms	Dissociation, agitation, depersonalisation, flat affect, hypervigilance, suspiciousness, thinking abnormal
	Psychosis	Hallucination, paranoia
Non-specific Mental		Emotional disorder, mental status changes, binge eating, communication disorder, frustration, psychiatric symptom,

Disorders	eating disorder

3) The Cognitive Disorders special topic consisting of the following subtopics, categories, and preferred terms:

Subtopic	Category	Preferred Terms
Cognitive	Attention disorders	Disturbance in attention, lethargy
	Thinking disorders	Disorientation, mental impairment, cognitive disorder, confusional state, bradyphrenia, thinking abnormal
	Memory disorders	Memory impairment, amnesia
	Somnolence	Somnolence, sedation, hypersomnia
Dizziness and Syncope	Dizziness	Dizziness, dizziness postural, presyncope
	Syncope	Syncope, altered state of consciousness, loss of consciousness

4) The Renal Disorders special topic consisted of the following subtopics and preferred terms:

Subtopic	Preferred Terms
Kidney Function	Blood creatinine increased, pollakiuria, blood creatinine abnormal, oliguria, blood urea increased, polyuria, urine output decreased, micturition frequency decreased, renal function test abnormal
Nephrolithiasis	Nephrolithiasis, calculus ureteric, renal stone removal, ureteral spasm, ureteral stent insertion, pelvic-ureteric obstruction
Urinalysis	Haematuria, blood urine present, urine colour abnormal, urine analysis abnormal
Urinary Infections	Urinary tract infection, kidney infection, white blood cells urine positive, dysuria, urine leukocyte esterase, bacteria urine
Lesions	Renal neoplasm

5) The Liver and Gallbladder special topic consisted of the following subtopics, categories, and preferred terms:

Subtopic	Category	Preferred Terms
Potential Hepatotoxicity	Alkaline Phosphatase	Blood alkaline phosphatase increased
	Bilirubin	Blood bilirubin unconjugated increased, bilirubin conjugated increased, blood bilirubin abnormal, blood bilirubin increased

	Transaminase	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hepatic function abnormal, liver function test abnormal, hepatitis cholestatic, alanine aminotransferase abnormal, tranasaminases increased
Gallbladder	Cholelithiasis	Cholelithiasis, biliary colic, gallbladder disorder, gallbladder pain, laparoscopic surgery
	Cholecystitis	Cholecystitis, cholecystitis chronic, cholecystitis acute
Liver	Lesions	Hepatic steatosis, haemangioma of liver, hepatic lesion, hepatomegaly, hepatic cyst

6) The Hypersensitivity Reaction/Skin Rash special topic consisted of the following subtopics, categories, and preferred terms:

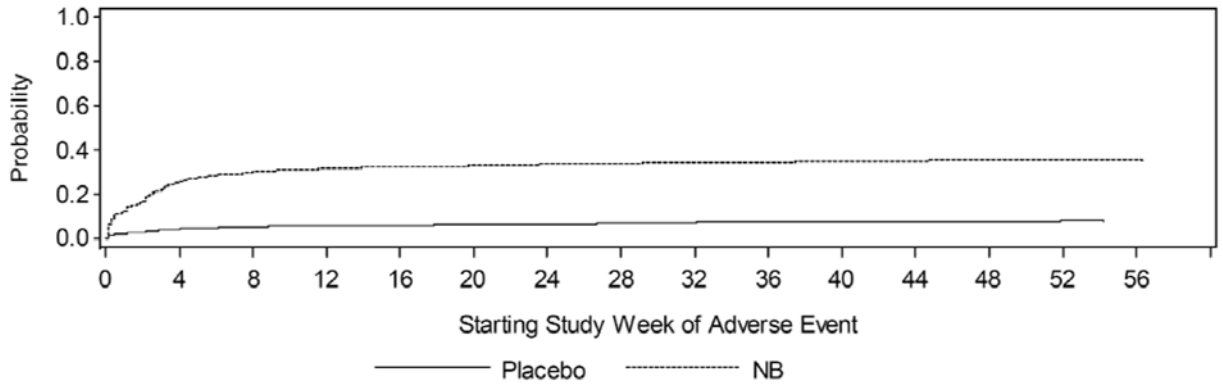
Subtopic	**Category**	**Preferred Terms**
Systemic Reactions	Anaphylaxis/ angioedema	Lip swelling, swelling face, angioedema, swollen tongue, oedema mouth, pharyngeal oedema, throat tightness, anaphylactic reaction
	Potential allergic symptoms	Cough, chest discomfort, dyspnoea, oedema peripheral, asthma, conjunctivitis, hypersensitivity, flushing, bronchospasm, swelling, oedema, wheezing, adverse drug reaction, bronchial hyperreactivity, cheilitis, eosinophil count increased, hyperventilation, laryngeal inflammation, allergic cough, generalised oedema, oral pruritus
Skin Reactions	Blistering	Blister, oropharyngeal blistering
	Rash	Rash, pruritus, rash erythematous, dermatitis, erythema, dermatitis allergic, rash generalised, rash pruritic, rash maculo-papular, pruritus generalised, drug eruption, rash macular, ulcerative keratitis, rash papular
	Urticaria	Urticaria
Local Reactions		Eye swelling, local swelling, sneezing, rhinitis allergic, conjunctivitis allergic, eye allergy, eyelid oedema, ocular hyperaemia, eye pruritus, scleral hyperaemia

APPENDIX E Time Dependency for Adverse Events

Time to Onset and Resolution for Selected Events (Nausea, Constipation, Headache, Vomiting, Dizziness, Anxiety, Hypertension, and Depression)

Nausea: The cumulative probability (estimated using the Kaplan- Meier method) of reporting nausea is greater for the Total NB group than the placebo group and the difference between groups was most apparent within the first 4 weeks of treatment and remained constant for the remainder of the double-blind treatment period.

Figure 14: Time to Onset of Adverse Event – Nausea: Primary Dataset, Double-Blind Treatment Phase



Data Source: Applicant's Figure ISS.P.1-3.1.3.
Abbreviations: NB=all doses of combination naltrexone and bupropion treatment.
Subjects who do not have AE of nausea before or on the last confirmed dose date +7 days are right-censored at last confirmed dose date. Event probabilities are based on the Kaplan-Meier method.

The median time to onset of nausea was shorter among NB-treated subjects than placebo, and the median duration of events was slightly longer among NB-treated subjects than placebo. A greater proportion of NB-treated subjects than placebo-treated subjects discontinued study medication due to nausea. In both placebo and NB groups, of those who discontinued due to nausea, the majority had events that resolved after discontinuation of study medication.

Table 66: Characterization of Nausea, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Preferred Term	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Nausea	**102 (6.7%)**	**1030 (31.8%)**
Median time to onset (weeks)	3.4	2.0
Median duration (weeks)	1.0	1.7
Subjects with event resulting in discontinuation from study medication	3 (2.9%)	203 (19.7%)
Subjects with event that resolved on or prior to discontinuation from study medication	1 (33.3%)	43 (21.2%)
Subjects with event that resolved after discontinuation from study medication	2 (66.7%)	143 (70.4%)
Subjects with event that persisted after discontinuation from study medication	0	17 (8.4%)
Study Disposition subsequent to discontinuation from study		

medication		
Completed	1 (33.3%)	57 (28.1%)
Withdrew	2 (66.7%)	146 (71.9%)
Adverse event	0	32 (21.9%)
Lost to follow up	0	25 (17.1%)
Other	2 (100.0%)	34 (23.3%)
Withdrawal of consent	0	55 (37.7%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

Constipation: The cumulative probability (estimated using the Kaplan- Meier method) of reporting constipation is greater for the Total NB group than the placebo group and the difference between groups was most apparent within the first 12 weeks of treatment and remained constant for the remainder of the double-blind treatment period.

The median time to onset of constipation was shorter among NB-treated subjects than placebo, although the median duration of events was longer. Overall, a greater proportion of NB-treated subjects than placebo-treated subjects discontinued study medication due to constipation. Of those who discontinued due to constipation, the majority had events that resolved after discontinuation of study medication.

Table 67: Characterization of Constipation, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Preferred Term	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Constipation	**109 (7.2%)**	**587 (18.1%)**
Median time to onset (weeks)	7.1	3.3
Median duration (weeks)	7.4	11.0
Subjects with event resulting in discontinuation from study medication	1 (0.9%)	13 (2.2%)
Subjects with event that resolved on or prior to discontinuation from study medication	0	1 (7.7%)
Subjects with event that resolved after discontinuation from study medication	1 (100%)	8 (61.5%)
Subjects with event that persisted after discontinuation from study medication	0	4 (30.8%)
Study Disposition subsequent to discontinuation from study medication		
Completed	0	1 (7.7%)
Withdrew	1 (100 %)	12 (92.3%)
Adverse event	0	4 (33.3%)
Lost to follow up	0	0

Other	0	4 (33.3%)
Withdrawal of consent	1 (100 %)	4 (33.3%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

Headache

The median time to onset of headache was shorter among NB-treated subjects than placebo, although the median duration of events was similar. A greater proportion of NB-treated subjects than placebo-treated subjects discontinued study medication due to headache. In both placebo and NB groups, of those who discontinued due to nausea, the majority had events that resolved after discontinuation of study medication.

Table 68: Characterization of Headache, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Preferred Term	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Headache	**157 (10.4%)**	**554 (17.1%)**
Median time to onset (weeks)	4.1	2.6
Median duration (weeks)	1.6	1.7
Subjects with event resulting in discontinuation from study medication	9 (5.7%)	55 (9.9%)
Subjects with event that resolved on or prior to discontinuation from study medication	1 (11.1%)	7 (12.7%)
Subjects with event that resolved after discontinuation from study medication	6 (66.7%)	43 (78.2%)
Subjects with event that persisted after discontinuation from study medication	2 (22.2%)	5 (9.1%)
Study Disposition subsequent to discontinuation from study medication		
Completed	2 (22.2%)	10 (18.2%)
Withdrew	7 (77.8 %)	45 (81.8%)
Adverse event	0	8 (17.8%)
Lost to follow up	0	5 (11.1%)
Other	4 (57.1 %)	10 (22.2%)
Withdrawal of consent	3 (42.9 %)	22 (48.9%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

Vomiting: The cumulative probability (estimated using the Kaplan- Meier method) of reporting vomiting or dry mouth is greater for the Total NB group than the placebo group and the difference between groups was most apparent within the first 8 weeks of treatment and remained relatively constant for the remainder of the double-blind treatment period.

The median time to onset of vomiting was shorter among NB-treated subjects than placebo, although the median duration of events was similar. A greater proportion of NB-treated subjects than placebo-treated subjects discontinued study medication due to vomiting. Of those who discontinued due to vomiting, the majority had events that resolved after discontinuation of study medication.

Table 69: Characterization of Vomiting, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Preferred Term	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Vomiting	**44 (2.9%)**	**321 (9.9%)**
Median time to onset (weeks)	12.9	3.9
Median duration (weeks)	0.3	0.3
Subjects with event resulting in discontinuation from study medication	1 (2.3%)	35 (10.9%)
Subjects with event that resolved on or prior to discontinuation from study medication	0	13 (37.1%)
Subjects with event that resolved after discontinuation from study medication	1 (100 %)	21 (60.0%)
Subjects with event that persisted after discontinuation from study medication	0	1 (2.9%)
Study Disposition subsequent to discontinuation from study medication		
Completed	0	7 (20.0%)
Withdrew	1 (100 %)	28 (80.0%)
Adverse event	0	9 (32.1%)
Lost to follow up	1 (100 %)	5 (17.9%)
Other	0	5 (17.9%)
Withdrawal of consent	0	9 (32.1%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

Dizziness: The cumulative probability (estimated using the Kaplan-Meier method) of reporting dizziness is greater for the Total NB group than the placebo group and the difference between groups was most apparent within the first 4 weeks of treatment and remained constant for the remainder of the double-blind treatment period.

The median time to onset of dizziness was shorter among NB-treated subjects than placebo, although the median duration of events was similar. A greater proportion of NB-treated subjects than placebo-treated subjects discontinued study medication due to dizziness. Of those who discontinued due to dizziness, the majority had events that resolved after discontinuation of study medication.

Table 70: Characterization of Dizziness, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Preferred Term	**Placebo (N=1515) n (%)**	**Total NB (N=3239) n (%)**
Dizziness	**51 (3.4%)**	**311 (9.6%)**
Median time to onset (weeks)	6.0	2.1
Median duration (weeks)	1.1	1.3
Subjects with event resulting in discontinuation from study medication	5 (9.8%)	42 (13.5%)
Subjects with event that resolved on or prior to discontinuation from study medication	2 (40 %)	11 (26.2%)
Subjects with event that resolved after discontinuation from study medication	2 (40 %)	27 (64.3%)
Subjects with event that persisted after discontinuation from study medication	1 (20 %)	4 (9.5%)
Study Disposition subsequent to discontinuation from study medication		
Completed	0	6 (14.3%)
Withdrew	5 (100 %)	36 (85.7%)
Adverse event	0	6 (16.7%)
Lost to follow up	0	6 (16.7%)
Other	2 (40%)	12 (33.3%)
Withdrawal of consent	3 (60%)	12 (33.3%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

Anxiety

The median time to onset of anxiety was shorter among NB-treated subjects than placebo, as was the median duration of events. A greater proportion of NB-treated subjects than placebo-treated subjects discontinued study medication due to anxiety. Of those who discontinued due to anxiety, the majority had events that resolved after discontinuation of study medication.

Table 71: Characterization of Anxiety, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Preferred Term	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Anxiety	**43 (2.8%)**	**127 (3.9%)**
Median time to onset (weeks)	11.4	3.0
Median duration (weeks)	4.1	2.1
Subjects with event resulting in discontinuation from study medication	10 (23.3%)	21 (16.5%)
Subjects with event that resolved on or prior to discontinuation from study medication	0	4 (19.0%)
Subjects with event that resolved after discontinuation from study medication	6 (60 %)	13 (61.9%)
Subjects with event that persisted after discontinuation from study medication	4 (40 %)	4 (19.0%)
Study Disposition subsequent to discontinuation from study medication		
Completed	4 (40%)	7 (33.3%)
Withdrew	6 (60 %)	14 (66.7%)
Adverse event	0	7 (50.0%)
Lost to follow up	0	1 (7.1%)
Other	2 (33.3%)	1 (7.1%)
Withdrawal of consent	4 (66.7%)	5 (35.7%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

Hypertension

The median time to onset of hypertension was shorter among NB-treated subjects than placebo, although the median duration of events was longer. Eleven 11 NB-treated subjects and 0 placebo-treated subjects discontinued study medication due to hypertension. Of those NB subjects who discontinued due to hypertension, 46% had events that resolved after discontinuation of study medication.

Table 72: Characterization of Hypertension, Double-Blind Treatment Phase, Primary Placebo-Controlled Integrated Dataset

Preferred Term	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Hypertension	**34 (2.2%)**	**94 (2.9%)**
Median time to onset (weeks)	25.3	17.0
Median duration (weeks)	8.0	9.6
Subjects with event resulting in discontinuation from study	0	11 (11.7%)

Preferred Term	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
medication		
Subjects with event that resolved on or prior to discontinuation from study medication	0	2 (18.2%)
Subjects with event that resolved after discontinuation from study medication	0	5 (45.5%)
Subjects with event that persisted after discontinuation from study medication	0	4 (36.4%)
Study Disposition subsequent to discontinuation from study medication		
Completed	0	3 (27.3%)
Withdrew	0	8 (72.7%)
Adverse event	0	1 (12.5%)
Lost to follow up	0	0
Other	0	4 (50 %)
Withdrawal of consent	0	3 (37.5%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

Depression

The median time to onset of depression was shorter among NB-treated subjects than placebo and the median duration of events was slightly shorter among NB-treated subjects than placebo. A slightly higher proportion of placebo-treated subjects discontinued study medication due to depression than NB-treated subjects. Of those who discontinued due to depression, 62% of the placebo-treated subjects and 56% of the NB-treated subjects had events that resolved after discontinuation of study medication.

Table 73: Characterization of Depression, Double-Blind Treatment Phase Primary Placebo-Controlled Integrated Dataset

Preferred Term	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Depression	**23 (1.5%)**	**34 (1.0%)**
Median time to onset (weeks)	8.0	4.3
Median duration (weeks)	3.1	2.1
Subjects with event resulting in discontinuation from study medication	13 (56.5%)	16 (47.1%)
Subjects with event that resolved on or prior to discontinuation from study medication	0	1 (6.3%)
Subjects with event that resolved after discontinuation from study medication	8 (61.5%)	9 (56.3%)

Subjects with event that persisted after discontinuation from study medication	5 (38.5%)	6 (37.5%)
Study Disposition subsequent to discontinuation from study medication		
Completed	4 (30.8%)	4 (25.0%)
Withdrew	9 (69.2%)	12 (75.0%)
Adverse event	2 (22.2%)	2 (16.7%)
Lost to follow up	4 (44.4%)	1 (8.3%)
Other	1 (11.1%)	3 (25 %)
Withdrawal of consent	2 (22.2%)	6 (50%)

Source: Excerpts from Orexigen Table 26Jul2010 - 13-14.1
The percentage of subjects with an event resulting in discontinuation of study medication is calculated based on the total number of subjects with a specific AE. The percentage of subjects with a given AE status (e.g. resolved or persisted) and percentage related to study disposition subsequent to discontinuation from study medication are calculated based on the number of subjects with an event resulting in discontinuation of study medication. The AE categories under withdrew (e.g. adverse event, lost to follow up, etc.) are calculated based on the numbers of subjects that withdrew from the study subsequent to discontinuation from study medication.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

Advisory Committee Briefing Document: Statistical Review of Efficacy
Advisory Committee Date: December 7, 2010

NDA/Serial Number:	200063/0
Drug Name:	Contrave™ (naltrexone / bupropion) extended-release tablets
Indication(s):	Weight management
Applicant:	Orexigen
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewers	J. Todd Sahlroot, Team Leader and Deputy Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Eileen Craig, M.D., Medical Reviewer
	Eric Colman, M.D., Medical Team Leader and Deputy Division Director
Project Manager:	Meghna Jairath

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1. EXECUTIVE SUMMARY

1.1 Conclusions about efficacy

The results of four Phase 3 studies are consistent and confirm the efficacy of naltrexone 32 mg /bupropion 360 mg (NB32) compared to placebo after 56 weeks of treatment in three of the four studies and 28 weeks of treatment in one of the four studies (TABLE 1, TABLE 2). The co-primary endpoints were average weight loss compared to baseline and the percentage of subjects who lost at least 5% of baseline body weight. Results of alternate analysis models and other versions of the analysis population were consistent with the results from the primary analysis. The effect of naltrexone 16 mg /bupropion 360 mg (NB16), assessed in one study, was statistically significant and consistent with a dose-response relationship between NB16 and NB32.

TABLE 1 Phase 3 studies: Body weight (kg), percent change from baseline to week 56 endpoint (week 28 for Study NB-303); Full Analysis Set (LOCF)

	Group	n	Baseline mean (SD)	Percent Change from Baseline LSMean (SE)	LS Mean Difference from Placebo (95% CI)	p
Study NB-301 (week 56)	Placebo	511	99.3 (14.3)	-1.3 (0.3)		
Customary diet and	NB16	471	100.1 (14.4)	-5.9 (0.3)	-3.7 (-4.5, -2.9)	<0.001
behavior counseling	NB32	471	100.2 (16.3)	-6.1 (0.3)	-4.8 (-5.6, -4.0)	<0.001
Study NB-302 (week 56)	Placebo	193	101.9 (15.0)	-5.1 (0.6)		
Intensive lifestyle modification counseling	NB32	482	100.7 (15.4)	-9.3 (0.4)	-4.2 (-5.6, -2.9)	<0.001
Study NB-303 (week 28)	Placebo	456	99.3 (16.0)	-1.9 (0.3)		
Customary diet and behavior counseling	NB32	825	100.7 (16.7)	-6.5 (0.2)	-4.6 (-5.2, -3.9)	<0.001
Study NB-304 (week 56)	Placebo	159	105.0 (17.1)	-1.8 (0.4)		
Obese subjects with type 2 diabetes	NB32	265	106.5 (19.1)	-5.0 (0.3)	-3.3 (-4.3, -2.2)	<0.001

TABLE 2 Phase 3 studies; Body weight, proportion 5% responders at week 56 (week 28 for Study NB-303); Full Analysis Set (LOCF)

	Group	n	5% responders n(%)	Odds Ratio (vs. placebo)	95% CI of Odds Ratio	p
Study NB-301 (week 56)	Placebo	511	84 (16.4%)			
Customary diet and	NB16	471	186 (39.5%)	3.4	(2.5, 4.6)	<0.001
behavior counseling	NB32	471	226 (48.0%)	4.9	(3.6, 6.6)	<0.001
Study NB-302 (week 56)	Placebo	193	82 (42.5%)			
Intensive lifestyle modification counseling	NB32	482	320 (66.4%)	2.8	(2.0, 4.1)	<0.001
Study NB-303 (week 28)	Placebo	456	80 (17.5%)			
Customary diet and behavior counseling	NB32	825	459 (55.6%)	6.6	(5.0, 8.8)	<0.001
Study NB-304 (week 56)	Placebo	159	30 (18.9%)			
Obese subjects with type 2 diabetes	NB32	265	118 (44.5%)	3.4	(2.2, 5.5)	<0.001

A substantial percentage of randomized subjects in each study and study arm, between 41% and 51%, discontinued study drug prior to week 56. This poses a challenge to estimating the placebo-adjusted effect of the naltrexone /bupropion combination with respect to all randomized subjects. Several factors contributed to the tendency to discontinue study drug:

1. Nausea associated with the naltrexone /bupropion combination: The naltrexone /bupropion combination was associated with early discontinuation of study drug due to adverse events, more so than the placebo arm in each study. The median time to withdrawal due to adverse events was 4 weeks, which is the end of the titration period. The most frequently reported adverse event associated with the naltrexone /bupropion combination was nausea. Subjects who discontinued before week 4 were not likely to be included in the full analysis database, unless they scheduled an exit visit.

2. Insufficient weight loss: At any given time during the study, subjects who had lost less weight were more likely to discontinue than subjects who had lost more weight. This pattern is most evident in the first 28 weeks of each study.

3. Sufficient weight loss: Some subjects discontinued study medication in the later weeks of a study, after they had lost more than 5% of their baseline body weight.

These factors, taken together, complicate the statistical approach to representing the responses of subjects who discontinued study medication. There may not be one approach to estimating the placebo-adjusted effect of the naltrexone /bupropion combination that fully captures the dynamics of study discontinuation. For this reason, I believe it is useful to evaluate the range of estimates obtained from the sensitivity analysis.

1.2 Brief Overview of Clinical Studies

The applicant used the results from the Phase 2 studies, particularly Study NB-201, to support the contribution of naltrexone and bupropion separately to the overall efficacy of the combination product. This was acceptable to the Division and follows the advice in the *Guidance for Industry: Developing Products for Weight Management* (2007 draft). For a description of the results of Study NB-201, see Appendix A of this review.

This application includes the results from four Phase 3 studies. These studies evaluated the efficacy, safety and tolerability of naltrexone 32 mg /bupropion 360 mg and naltrexone 16 mg /bupropion 360 mg in obese and overweight subjects receiving customary diet and behavioral counseling, including prescribed exercise (Studies NB-301 and NB-303), in obese/overweight subjects undergoing intensive lifestyle modification counseling (Study NB-302), and in obese/overweight subjects with type 2 diabetes (Study NB-304). Studies NB-301, NB-302 and NB-303 enrolled subjects with a BMI $\geq$ 30 and $\leq$ 45 kg/m^2 for subjects with uncomplicated obesity, and with a BMI of $\geq$ 27 and $\leq$ 45 kg/m^2 for subjects with obesity and controlled hypertension and/or dyslipidemia. Study NB-304 enrolled obese/overweight subjects with type 2 diabetes (HbA1c > 7% and < 10%; not on injectable diabetes medications or inhaled insulin).

The number of subjects randomized in each study were as follows:

- Study NB-301: 1742 subjects were randomized; 578 to receive naltrexone 16 mg / bupropion 360 mg (NB16), 583 to receive naltrexone 32 mg / bupropion 360 mg (NB32) and 581 to receive placebo.

- Study NB-302: 793 subjects were randomized; 591 to receive NB32 and 202 to receive placebo.

- Study NB-303: 1496 subjects were randomized; 1001 to receive NB32 and 495 to receive placebo.

- Study NB-304: 505 subjects were randomized; 335 to receive NB32 and 170 to receive placebo.

Studies consisted of a screening period (up to 4 weeks), a 4-week titration period, and a 52-week maintenance period. Study visits occurred every 4 weeks. The primary endpoint for Study NB-303 occurred at week 28 rather than at week 56 because this study had a re-randomization protocol that started at week 28 and continued through week 44. During this period, subjects who were randomized to receive NB32 and who failed to achieve or maintain a 5% reduction in body weight were re-randomized to either continue treatment with NB32 or have their dose increased to naltrexone 48 mg /bupropion 360 mg. Because of this differential treatment of randomized arms, the Division requested that the primary endpoint be determined at week 28, with results from week 56 providing supportive information.

1.3 Statistical Issues and Findings

A substantial percentage of randomized subjects in each study and study arm, between 41% and 51%, discontinued from taking study medication prior to week 56 (TABLE 5). This level of discontinuation is typical of weight loss studies. The estimate of the placebo-adjusted effect of the naltrexone /bupropion combination needs to be evaluated in the context of this high level of discontinuation. The naltrexone /bupropion combination was associated with early discontinuation due to adverse events, more so than the placebo arm in each study (TABLE 5). The most frequently reported adverse event associated with the naltrexone /bupropion combination was nausea (TABLE 5). The median time to discontinuation due to adverse events was 4 weeks in each study, which is the end of the titration period. Subjects who discontinued before week 4 were not likely to be included in the full analysis database, unless they scheduled an exit visit. The full analysis set was not likely to capture the experiences of subjects who discontinued very early due to nausea with the naltrexone /bupropion combination.

Most of the subjects who discontinued study medication did so before the week 26 mid-point (FIGURE 1). On average, subjects who discontinued early had lost less weight at the time of withdrawal, compared to the average weight loss at the same study week in subjects who completed the study (FIGURE 2-FIGURE 5). This trend was apparent in both the placebo and the naltrexone /bupropion arms. My interpretation of this finding is that at any given time

throughout the study, subjects who were less successful at losing weight were more likely to discontinue than subjects who were more successful. Based on this interpretation, the completers are likely to be different from the non-completers with respect to the efficacy endpoint.

However, some subjects discontinued study medication in the later weeks of a study, after having lost more than 5% of their baseline body weight (FIGURE 2-FIGURE 5). For this reason, classifying all study dropouts as 5% non-responders may not fully represent the response to the naltrexone / bupropion combination.

In my opinion, the applicant used a reasonable set of analyses that explored the effect of different analysis sets and analysis models on the study conclusions. The sensitivity analysis included plausible interpretations of the weight response of subjects who discontinued.

2. INTRODUCTION

2.1 Overview

Contrave® (naltrexone HCL and bupropion HCL) Sustained-Release tablets is intended for the treatment of obesity, including weight loss and weight management. Contrave is a combination product of naltrexone and bupropion. Naltrexone is approved for the treatment of opiate and alcohol dependence. Bupropion is approved for the treatment of major depression and nicotine dependence. Bupropion is known to cause weight loss when used for its currently approved indications. The applicant, Orexigen, based the development of the combination product on the hypothesis that the use of the two drugs in combination would lead to greater weight loss than would be seen with either naltrexone or bupropion alone[1]. The proposed daily dose of Contrave is 32 mg naltrexone / 360 mg bupropion.

The applicant proposes the following indication: "Contrave 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. Contrave is recommended for patients with an initial body mass index $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension."

2.2 Scope of Statistical Review of Efficacy for Advisory Committee Meeting on December 7, 2010

The purpose of this portion of the briefing document is to provide the statistical review perspective of the efficacy of Contrave, based on the results from four Phase 3 studies: NB-301, NB-302, NB-303, and NB-304. The applicant used the results from the Phase 2 studies, particularly Study NB-201, to support the contribution of naltrexone and bupropion separately to the overall efficacy of Contrave. This was acceptable to the Division and follows the advice in the *Guidance for Industry: Developing Products for Weight Management* (2007 draft). A brief summary of results from Study NB-201 is included in Statistical Review Appendix A of this portion of the briefing document.

The four Phase 3 studies that are described in this submission evaluated the efficacy, safety and tolerability of NB in obese and overweight subjects receiving customary diet and behavioral counseling, including prescribed exercise (Studies NB-301 and NB-303), in obese/overweight subjects undergoing intensive lifestyle modification counseling (Study NB-301), and in obese/overweight subjects with type 2 diabetes (Study NB-304). Studies NB-301, NB-302 and NB-303 enrolled subjects with a BMI $\geq$ 30 and $\leq$ 45 kg/m^2 for subjects with uncomplicated obesity, and with a BMI of $\geq$ 27 and $\leq$ 45 kg/m^2 for subjects with obesity and controlled hypertension and/or dyslipidemia. A more detailed description of each study is shown below:

- Study NB-301 was conducted in male and female subjects between 18 to 65 years of age with either uncomplicated obesity or with obesity/overweight with controlled hypertension

[1] The source of this paragraph (paraphrased) is Part 2.2 (Introduction) of this NDA submission

and/or dyslipidemia. A total of 1742 subjects were randomized to receive naltrexone 16 mg / bupropion 360 mg (NB15; n=578), naltrexone 32 mg / bupropion 360 mg (NB32; n=583) or placebo (n=581). The study consisted of four periods: a screening period of up to 4 weeks (at least 2 visits), a titration period of 4 weeks (1 visit; TABLE 3); a study drug maintenance period of 52 weeks (14 visits), and a drug discontinuation period of 2 weeks (1 visit) for a total of 58 weeks of study duration. Subjects were to be seen every 4 weeks from baseline to week 56, and at week 58 following the 2-week drug discontinuation period. Subjects received ancillary therapy every 12 weeks consisting of diet instruction and advice on behavior modification and exercise. Subjects who terminated study drug treatment before week 56 were encouraged to return for their scheduled visits to be weighed and for a waist circumference measurement at week 28 and week 56, as appropriate. The study was conducted at 34 sites in the U.S, from 10/4/07 (first patient enrolled) to 5/26/09 (last patient completed).

- Study NB-302 was conducted in male and female subjects between 18 to 65 years of age with either uncomplicated obesity or with obesity/overweight with controlled hypertension and/or dyslipidemia. A total of 793 subjects were randomized to receive NB32 (n=591) or placebo (n=202). The study consisted of a screening period (up to 4 weeks; TABLE 3), a 4-week titration period, and a 52-week maintenance period. Subjects also participated in an intense behavior modification program that included dietary instructions, twenty-eight 90-minute group sessions, and prescribed exercise. Subjects who prematurely discontinued study drug were encouraged to continue participation in the behavior modification program and to return to the study center for a body weight measurement (every 4 weeks) and waist circumference measurement (weeks 28 and 56). The study was conducted at 9 sites in the U.S, from 3/7/07 (first patient enrolled) to 9/12/08 (last patient completed).

- Study NB-303 was conducted in male and female subjects between 18 to 65 years of age with uncomplicated obesity or with obesity/overweight with controlled hypertension and/or dyslipidemia. There were 495 subjects randomized to receive placebo and 1001 randomized to receive NB32. The study consisted of a screening period (up to 4 weeks), a 4-week titration period, and a 52-week maintenance period. Subjects assigned to NB32 were randomized within each study center (1:1 ratio) to two alternative dosage schedules for naltrexone, "fast" or "slow" (TABLE 3). For subjects in the fast titration group, the initial daily dose of naltrexone was 8 mg, which was increased by 8 mg each week until reaching 32 mg at week 4. For subjects in the slow titration group, the initial daily dose of naltrexone was 4 mg, which was increased by 4 mg each week until reaching 16 mg at week 4. The dose was increased to 32 mg at week 5. Subjects received ancillary therapy consisting of diet instruction and advice on behavior modification and exercise.

  Study visits occurred every 4 weeks. Beginning at week 28 through week 44, subjects randomized to receive NB32 who failed to achieve or maintain a 5% reduction in body weight were re-randomized to either continue treatment with NB32 or have their dose increased to naltrexone 48 mg / bupropion 360 mg (NB48). Subjects not re-randomized at Week 28 but who did not maintain at least 5% of baseline body weight loss during Weeks 32-44 were also re-randomized. Subjects were only re-randomized once. Subjects also received ancillary therapy consisting of dietary instruction and advice on behavior

modification and exercise. The study was conducted at 36 sites in the U.S, from 12/6/07 (first patient enrolled) to 6/8/09 (last patient completed).

- Study NB-304 was conducted in obese/overweight subjects between 18 and 70 years of age with type 2 diabetes (HbA1c > 7% and < 10%; not on injectable diabetes medications or inhaled insulin). The safety and efficacy of a total daily dose of NB32 was compared to placebo. A total of 505 subjects were randomized to receive NB32 (n=335) or placebo (n=170). The study consisted of a screening period (up to 4 weeks), a 4-week titration period (TABLE 3), and a 52-week maintenance period. All subjects received ancillary therapy at baseline and weeks 4, 16, 28 and 40 consisting of diet instruction, advice on behavior modification, and physical activity suggestions. Subjects who prematurely discontinued study drug were encouraged to return to the study center for a body weight measurement (every 4 weeks) and waist circumference measurement (weeks 28 and 56). The study was conducted at 53 sites in the U.S, from 5/29/07 (first patient enrolled) to 6/1/09 (last patient completed).

TABLE 3 Naltrexone / bupropion and placebo dosing daily during the titration and maintenance of the four Phase 3 studies

Group	Studies	Titration Naltrexone (mg) / Bupropion (mg) Week 1 Days 1-7	Week 2 Days 8-14	Week 3 Days 15-21	Week 4 Days 22-28	Maintenance Weeks 5- 56
NB16	NB-301, NB-303	4 / 90	8 / 180	12 / 270	16 / 360	16 / 360
NB32fast	NB-301, NB-302, NB-303, NB-304	8 / 90	16 / 180	24 / 270	32 / 360	32 / 360
NB32slow	NB-303	4 / 90	8 / 180	12 / 270	16 / 360	32 / 360
Placebo	NB-301, NB-302, NB-303, NB-304	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0

Sources: Table 1 in each Clinical Study Reports, Study NB-301, Study NB-302, Study NB-303 and Study NB-304

Number of subjects in each trial: The applicant developed the size of each study to address: (1) the evaluation of efficacy from two co-primary endpoints; and (2) a general evaluation of safety. A key resource was the *Guidance for Industry: Developing Products for Weight Management* (February 2007 draft).

(1) For the evaluation of efficacy: Following the weight management guidance, a patient's body weight after one year of treatment in relation to baseline body weight is expressed in two different ways, as co-primary endpoints:

Continuous endpoint: *the average weight loss at one year, expressed as a percentage change from baseline*

Categorical endpoint: *the percentage of patients who lost at least 5% of their baseline body weight at one year*

The applicant used the following estimates and assumptions in calculating the number of subjects needed in each study for a statistical evaluation of efficacy:

- Approximately 40% of randomized subjects would discontinue from the study prior to the week 52 endpoint, including 20% who would not provide any post-baseline data (and therefore not be included in the intention-to-treat population).

- For the continuous endpoint:
  - A placebo-adjusted treatment effect of 5% (based on results from Study NB-201)
  - A standard deviation of 7% for studies NB-301 and NB-303 and 5% for studies NB-302 and NB-304. I note that these estimates are consistent with the results from study NB-201.

- For the categorical endpoint:
  - A placebo-adjusted treatment effect of 14% (50% of placebo-treated subjects and 64% of Contrave-treated subjects meeting the categorical endpoint) in studies NB-301, NB-301 and NB-303. The response rate for placebo was assumed to be similar to the response rates observed for the lifestyle modification alone arm, as reported by Wadden et al (2005)[2].

  - A placebo-adjusted treatment effect of 12.5% (15% of placebo subjects and 27.5% of Contrave-treated subjects in Study NB-304, based on a clinical study of rimonabant in overweight or obese patients with Type 2 diabetes (Scheen et al., 2006)[3]

- A two-tailed α of 0.05 and a target of at least 90% power

(2) For the evaluation of safety: The weight management guidance suggests that "A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment." The total number of subjects who were expected to complete one year in the four Phase 3 studies, based on an estimated 40% dropout rate, was predicted to be 1830 for naltrexone / bupropion combinations and 855 for placebo (TABLE 4).

TABLE 4 Number of subjects planned and predicted to have 1-year exposure to naltrexone/bupropion combinations and placebo in the four Phase 3 studies

Study	Treatment Arm	Number Planned to Randomize	Predicted number in the ITT database (based on 20% with no post-baseline data)	Predicted Number to Have 1-year Exposure (based on 40% dropout rate)
NB-301	1. naltrexone 16mg / bupropion 360 mg	550	440	330
	2. naltrexone 32 mg / bupropion 360 mg	550	440	330
	3. placebo	550	440	330

[2] Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. NEJM 2005; 353;20: 2111-20

[3] Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. Lancet 2006; 368: 1660-72.

NB-302	1. naltrexone 32 mg / bupropion 360 mg	600	480	360
	2. placebo	200	160	120
NB-303	1. naltrexone 32 mg / bupropion 360 mg	1000	800	600
	2. placebo	500	400	300
NB-304	1. naltrexone 48 mg / bupropion 360 mg	350	280	210
	2. placebo	175	140	105
Total number of randomized subjects predicted to have 1-year exposure to naltrexone / bupropion:				1830
Total number of subjects predicted to have 1 year exposure to placebo:				855

Source: Summary by this reviewer

3. STATISTICAL EVALUATION

3.1. Subject disposition

Completing 56 weeks of treatment with study drug: The disposition event of interest in each Phase 3 study was the completion or withdrawal from 56 weeks of treatment with study drug. Study NB-303 also evaluated the completion of 28 weeks of study drug. Subjects were free to discontinue their participation in the study (i.e., withdraw consent) at any time and without prejudice to further treatment. The investigator was able to withdraw a subject because of a safety risk or adverse event. The study protocols listed reasons why a subject might have their study drug discontinued, including non-adherence to at least 70% of study drug for two consecutive months or discontinuation of study drug for any reason for a period of at least 15 consecutive days.

A substantial percentage of randomized subjects in each study and study arm, between 41% and 51%, discontinued from taking study medication prior to week 56 (TABLE 5). This percentage of subjects was fairly similar in the placebo arm and the combination arm(s) within each study (TABLE 5). A large percentage of early discontinuation is typical of weight loss studies. Investigators in this field have proposed and evaluated different ways to evaluate weight loss programs and/or drugs, given that a large percentage of subjects are likely to discontinue before the primary endpoint period.[4] The weight management guidance recommends estimating the effect of a drug by several different methods. This sensitivity analysis should reflect the time dynamics and reasons for early discontinuation.

The naltrexone/bupropion combination was associated with early discontinuation due to adverse events, more so than the placebo arm in each study (TABLE 5A). More subjects identified

[4] For example, see Gadbury, GL, CS Coffee and DB Allison, 2003: Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. Obesity Reviews 4: 175-184.

"adverse events" as their reason for discontinuing from the naltrexone/bupropion combination than any other reason. This finding is consistent across studies. Moreover, the median time to withdrawal due to adverse events was 4 weeks in each study, which is the end of the titration period (TABLE 5B). This was the earliest median time to withdrawal for any of the reasons for discontinuation. The slow titration schedule for the NB32 combination did not appear to delay the median time to withdrawal compared to the fast titration schedule (TABLE 3, TABLE 5B). Nausea was the most frequently cited reason for dropout due to adverse event in the naltrexone/bupropion arms, followed by headache and dizziness (TABLE 5C).

The re-randomization period in Study NB-303 which took place at weeks 28-44 involved 251 subjects in the NB32 group who had failed to achieve or maintain at least 5% body weight loss from baseline. Of these, 128 were assigned to continue with NB32, and 107 (83.5%) completed treatment; 123 were assigned to NB48 and 104 (84.6%) completed treatment. The most common reason for discontinuation of drug was loss to follow-up.

On average, subjects who withdrew from study medication early had lost less weight at the time of withdrawal, compared to the average weight loss at the same study visit in subjects who completed 56 weeks of study medication (FIGURE 2-FIGURE 5). To assess this pattern, I calculated the mean weight change at each study visit in subjects who had discontinued study medication in the interval between a given study visit and the previous study visit. I compared this mean weight change to the weight change at the given study visit by patients who completed 56 weeks of study medication. The difference between subjects who completed and subjects who withdrew from study medication is apparent both in the combination arm(s) and the placebo arm in each study (FIGURE 2-FIGURE 5). The difference in means between completers and withdrawals at any given visit appears to be fairly constant from week 4 up through week 28, which is the time frame for most withdrawals. From week 28 to week 56, the difference in means at any given visit appears to be more variable (FIGURE 2-FIGURE 5). This variability may reflect (1) the smaller numbers of patients who withdrew after week 28; and (2) different reasons for withdrawing from study mediation towards the end of a study rather than close to the start.

Study visits following discontinuation from study drug: In the event that a subject discontinued study drug treatment prior to week 56, the investigator made every effort to have the subject return as soon as possible for an early termination visit that included all assessments outlined for the week 56 visit. In addition, the investigator encouraged the subject to return for their scheduled visits to be weighed. The off-study drug weights were used in the intention-to-treat analysis population as a sensitivity analysis.

TABLE 5 Disposition in the four Phase 3 studies

Study NB-301 at week 56 Customary diet and behavioral counseling	**naltrexone 16mg / bupropion 360 mg**	**naltrexone 32 mg / bupropion 360 mg**	**placebo**	**Total**
A. Disposition				
Randomized	578	583	581	1742
Completed	284 (49.1%)	296 (50.8%)	290 (49.9%)	870 (49.9%)
Withdrawn:	294 (50.9%)	287 (49.2%)	291 (50.1%)	872 (50.1%)
Adverse events	*122 (21.1%)*	*112 (19.2%)*	*56 (9.6%)*	*290 (16.6%)*
Withdrew consent	*63 (10.9%)*	*60 (10.3%)*	*90 (15.5%)*	*213 (12.2%)*
Lost to follow-up	*76 (13.1%)*	*65 (11.1%)*	*66 (11.4%)*	*207 (11.9%)*
Insufficient weight loss	*12 (2.1%)*	*12 (2.1%)*	*40 (6.9%)*	*64 (3.7%)*
Other[1]	*21 (3.8%)*	*38 (6.5%)*	*39 (6.7%)*	*98 (5.6%)*
B. Median time on study (weeks) prior to withdrawal by reason for withdrawal				
Adverse events	*4*	*4*	*9*	
Withdrew consent	*13*	*12*	*12*	
Lost to follow-up	*7*	*5*	*9*	
Combined Other[2]	*12*	*23.5*	*14*	
C. Most frequently cited adverse events as the reason for withdrawal				
Nausea or Vomiting	*31*	*41*	*3*	
Headache	*9*	*5*	*4*	
Dizziness or Vertigo	*15*	*7*	*3*	

Table 8, continued **Study NB-302 at week 56** **Intensive program for behavior modification**	**naltrexone 32 mg / bupropion 360 mg**	**placebo**	**Total**
A. Disposition			
Randomized	591	202	793
Completed	342 (57.9%)	118 (58.4%)	460 (58.0%)
Withdrawn:	249 (42.1%)	84 (41.6%)	333 (42.0%)
Adverse events	*150 (25.4%)*	*25 (12.4%)*	*175(22.1%)*
Withdrew consent	*43 (7.3%)*	*24 (11.9%)*	*67 (8.4%)*
Lost to follow-up	*22 (3.7%)*	*17 (8.4%)*	*39 (4.9%)*
Insufficient weight loss	*3 (0.5%)*	*6 (3.4%)*	*9 (1.1%)*
Other[1]	*31 (5.2%)*	*12 (5.9%)*	*43 (5.4%)*
B. Median time on study (weeks) prior to withdrawal by reason for withdrawal			
Adverse events	*4*	*15*	
Withdrew consent	*16*	*22.5*	
Lost to follow-up	*5*	*15*	
Combined Other[2]	*21*	*25*	
C. Most frequently cited adverse events as the reason for withdrawal			
Nausea or Vomiting	*31*	*0*	
Headache	*5*	*1*	
Dizziness or Vertigo	*5*	*0*	

Table 8, continued **Study NB-303 at weeks 28 and 56** **Customary diet and behavioral counseling**	**naltrexone 32 mg / bupropion 360 mg**	**placebo**	**Total**
A. Disposition			
Randomized	1001	495	1496
Completed at week 28	619 (61.8%)	319 (64.4%)	
Withdrawn by week 28	382 (38.2%)	176 (35.6%)	
Completed at week 56	538 (53.7%)	267 (53.9%)	805 (53.8%)
Withdrawn by week 56:	463 (46.3%)	228 (46.1%)	691 (46.2%)
Adverse events	*241 (24.1%)*	*68 (13.7%)*	*309 (20.7%)*
Withdrew consent	*75 (7.5%)*	*56 (11.3%)*	*131 (8.8%)*
Lost to follow-up	*77 (7.7%)*	*48 (9.7%)*	*125 (8.4%)*
Insufficient weight loss	*19 (1.9%)*	*33 (6.7%)*	*52 (3.5%)*
Other[1]	*51 (5.1%)*	*23 (4.6%)*	*74 (4.9%)*
B. Median time on study (weeks) prior to withdrawal by reason for withdrawal			
Titration[3]*:*	*Fast*	*Slow*	
Adverse events	*4*	*4*	*9*
Withdrew consent	*9*	*12.5*	*12.5*
Lost to follow-up	*8*	*12*	*9*
Combined Other[2]	*14*	*18.5*	*16*
C. Most frequently cited adverse events as the reason for withdrawal			
Nausea or Vomiting	*68*	*1*	
Headache	*26*	*4*	
Dizziness or Vertigo	*12*	*1*	

Table 8, continued **Study NB-304 at week 56** **Obese subjects with type 2 diabetes**	**naltrexone 32 mg / bupropion 360 mg**	**placebo**	**Total**
A. Disposition			
Randomized	335	170	505
Completed	175 (52.2%)	100 (58.8%)	275 (54.5%)
Withdrawn:	160 (47.8%)	70 (41.2%)	230 (45.5%)
Adverse events	*98 (29.3%)*	*26 (15.3%)*	*124 (24.6%)*
Withdrew consent	*21 (6.3%)*	*15 (8.8%)*	*36 (7.1%)*
Lost to follow-up	*22 (6.6%)*	*15 (8.8%)*	*37 (7.3%)*
Insufficient weight loss	*5(1.5%)*	*6 (3.5%)*	*11 (2.2%)*
Other[1]	*14 (4.2%)*	*8 (4.7%)*	*22 (4.4%)*
B. Median time on study (weeks) prior to withdrawal by reason for withdrawal			
Adverse events	*4*	*11*	
Withdrew consent	*17*	*30*	
Lost to follow-up	*5*	*13*	
Combined Other[2]	*15*	*17*	
C. Most frequently cited adverse events as the reason for withdrawal			
Nausea or Vomiting	*42*	*0*	
Headache	*6*	*0*	
Dizziness or Vertigo	*4*	*1*	

Notes:

[1] The "Other" category is a combination of categories identified by the applicant: drug non-compliance, failure to comply with protocol requirements, subject moved, subject became pregnant, enrolled but did not meet selection criteria, other primary reason, randomized but study drug not dispensed, death, and other primary reason not listed.

[2] The "Combined Other" category includes all of the categories from "Other" and "Insufficient weight loss."

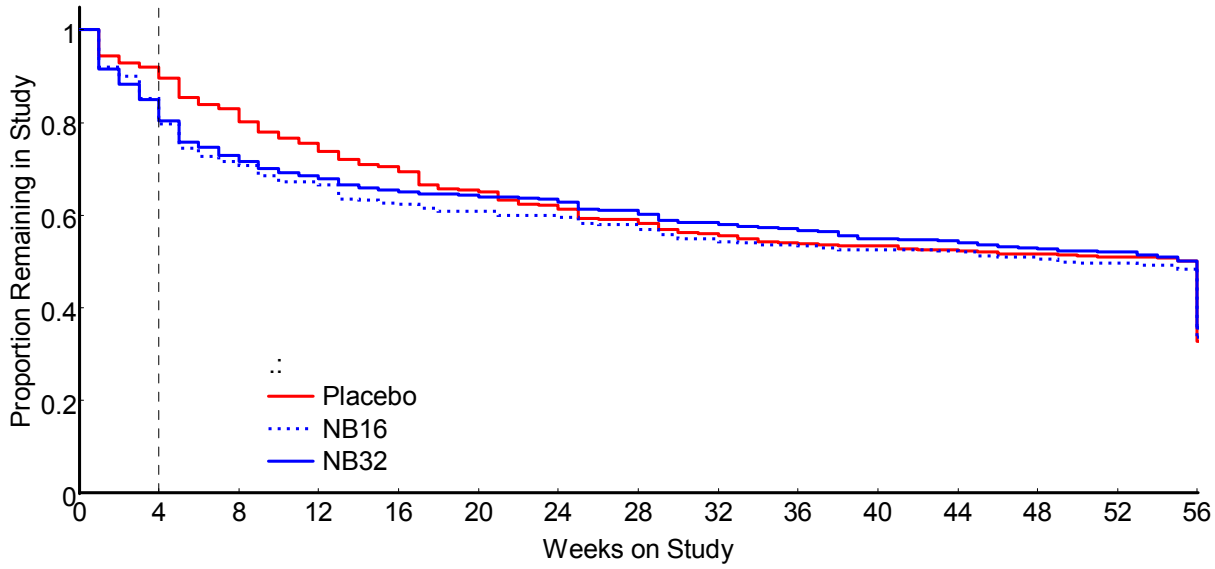
[3] Subjects assigned to NB32 in Study NB-303 were randomly allocated within center to two schedules of dose titration, "fast" and "slow" as described in Part 2.2.2 of this review.

Sources:

Tables ISE.301.101, ISE.302.1-1, ISE303.1-1 and ISE304.1-1, and analysis by this reviewer

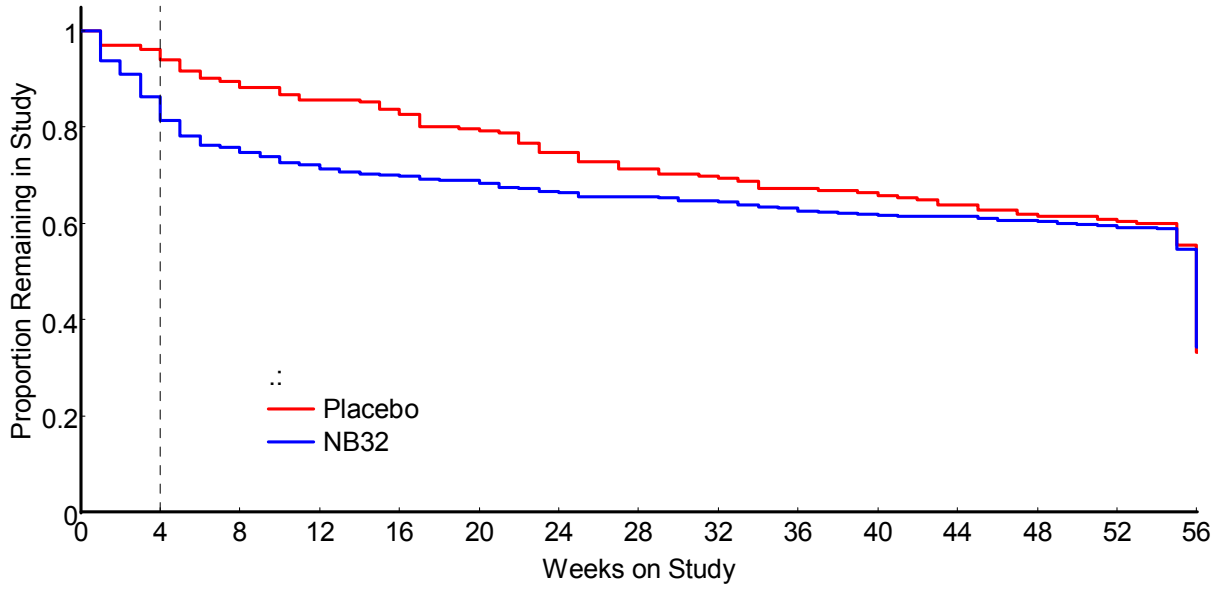
FIGURE 1 Disposition by week on study; Kaplan-Meier plots for Study NB-301, NB-302, NB-303 and NB-304

Study NB-301: Customary diet and behavioral counseling



Note for Study NB-301: The dashed gridline at week 4 represents the end of the drug titration period.

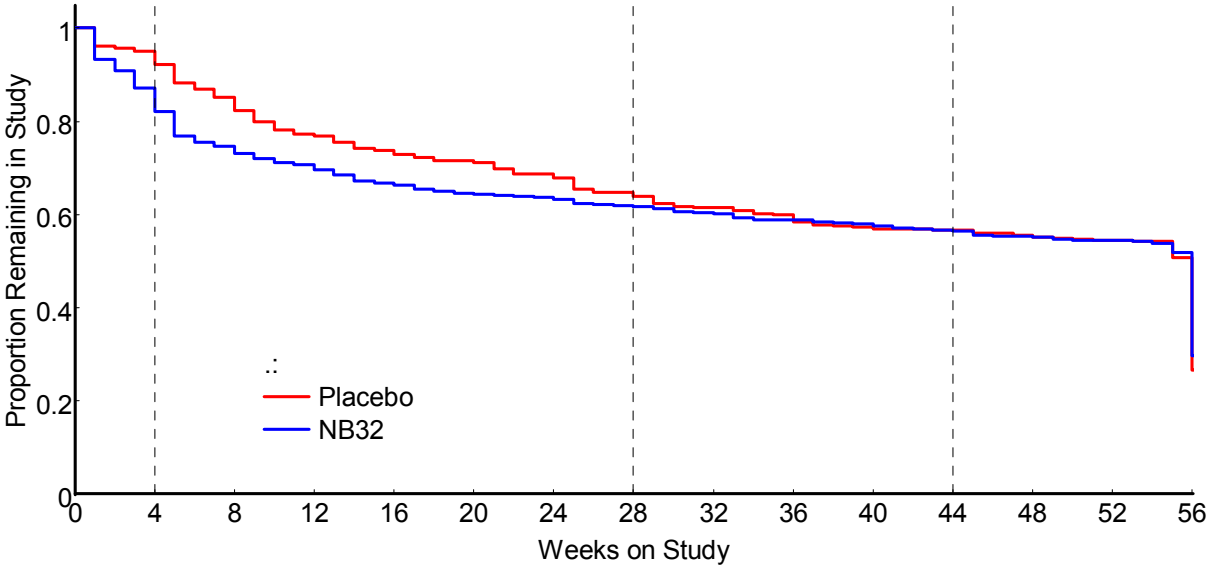
Study NB-302: Intensive program for behavior modification



Note for Study NB-302: The dashed gridline at week 4 represents the end of the drug titration period.

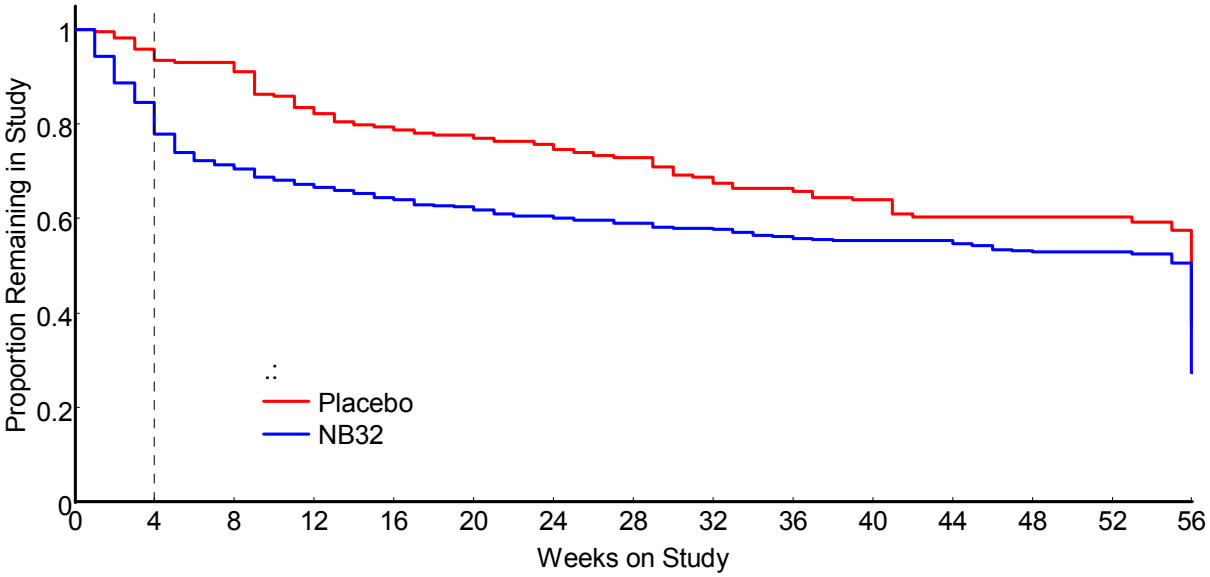
Figure 1, continued

Study NB-303: Customary diet and behavioral counseling



Notes for Study NB-303: The dashed gridline at week 4 represents the end of the drug titration period. From weeks 28-44, NB32-treated subjects who failed to achieve or maintain at least 5% of body weight loss from baseline were re-randomized (1:1 ratio) to continue NB32 or receive NB48. Subjects were re-randomized only once.

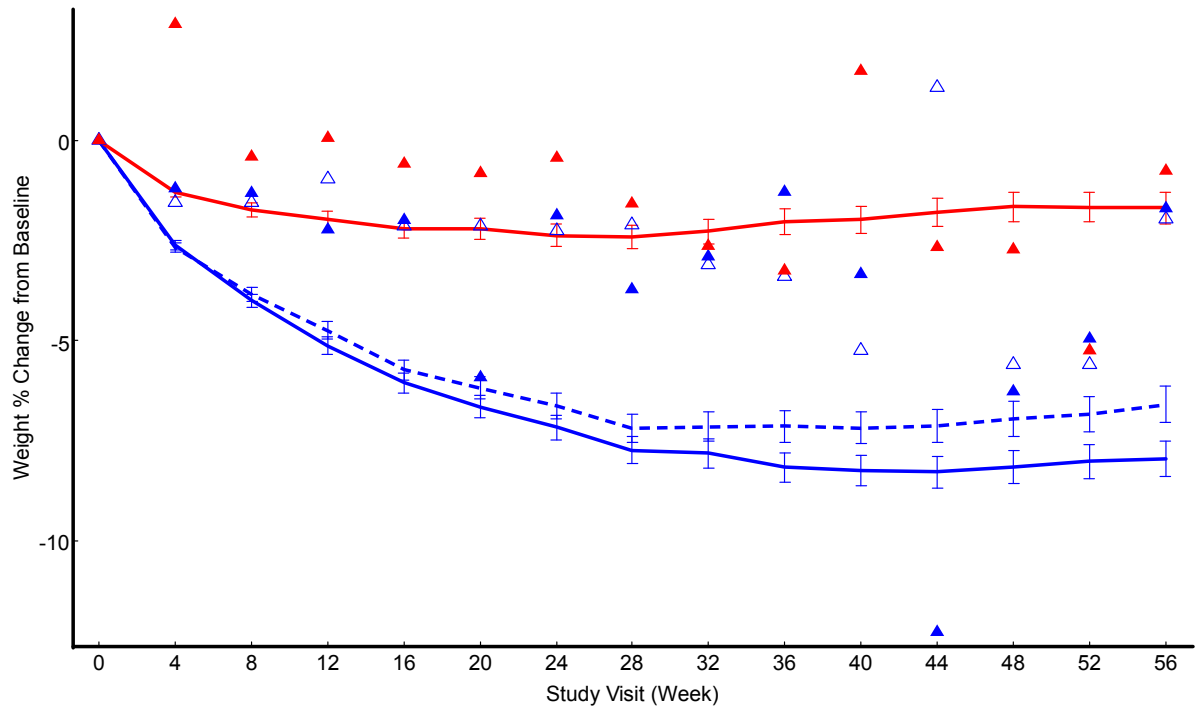
Study NB-304: Obese subjects with type 2 diabetes



Notes for Study NB-304: The dashed gridline at week 4 represents the end of the drug titration period.

Source: Analysis by this reviewer

FIGURE 2 Study NB-301; For subjects who completed 56 weeks of study medication, mean weight change at each study visit. For subjects who discontinued, mean weight change at the study visit prior to discontinuation

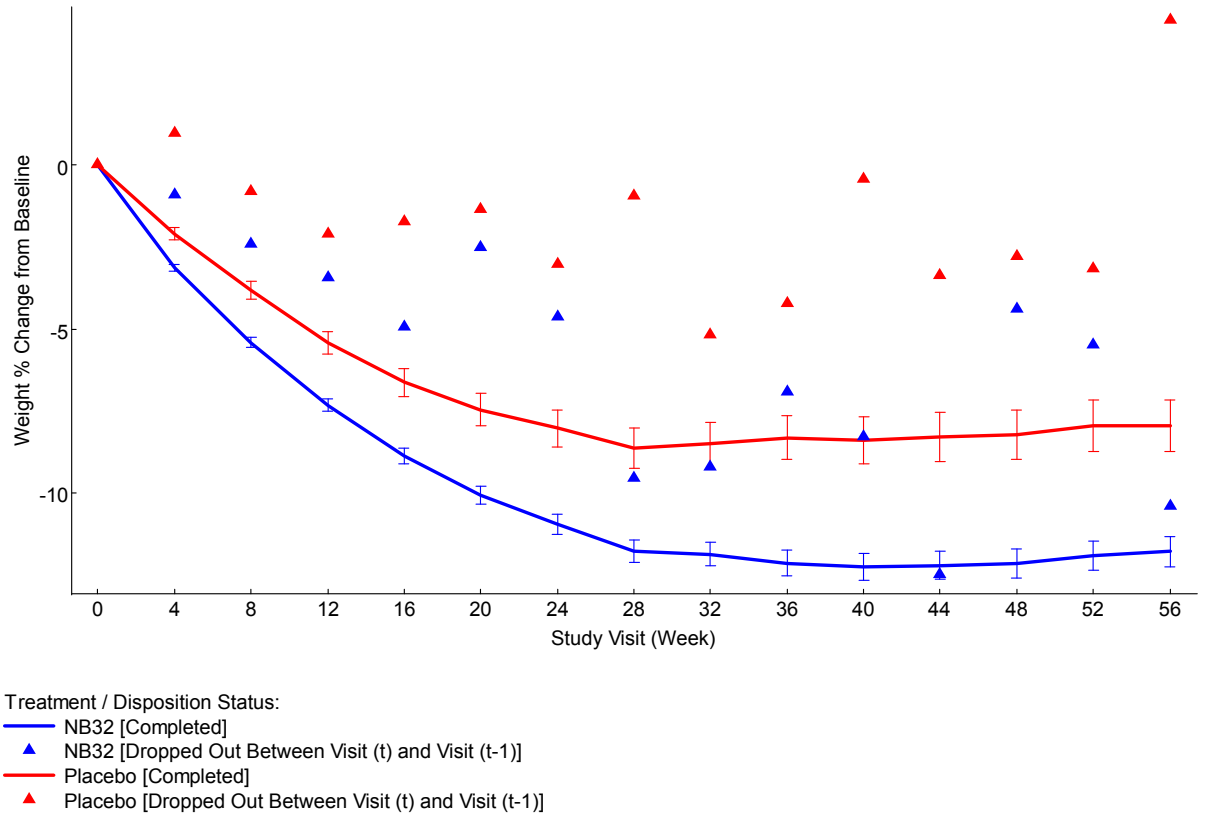


Notes:

- For subjects who stayed on study medication through week 56, the mean ± SEM is shown as a longitudinal profile. Subjects who completed study medication had treatment durations of 55-61 weeks in the efficacy database provided by the applicant (variable TRTDURWK).
- Single symbols represent the mean of subjects who discontinued in the time interval between the previous study visit (t-1) and the given study visit (t). A small number of subjects who were classified as "did not complete" study medications had treatment durations of 53-57 weeks: 3 in the NB16 arm, 8 in the NB32 arm, and 6 in the placebo group (variable TRTDURWK). This may represent errors in the database.
- The dose titration period was week 0 through week 4.

Source: Analysis by this reviewer

FIGURE 3 Study NB-302; For subjects who completed 56 weeks of study medication, mean weight change at each study visit. For subjects who discontinued, mean weight change at the study visit prior to discontinuation

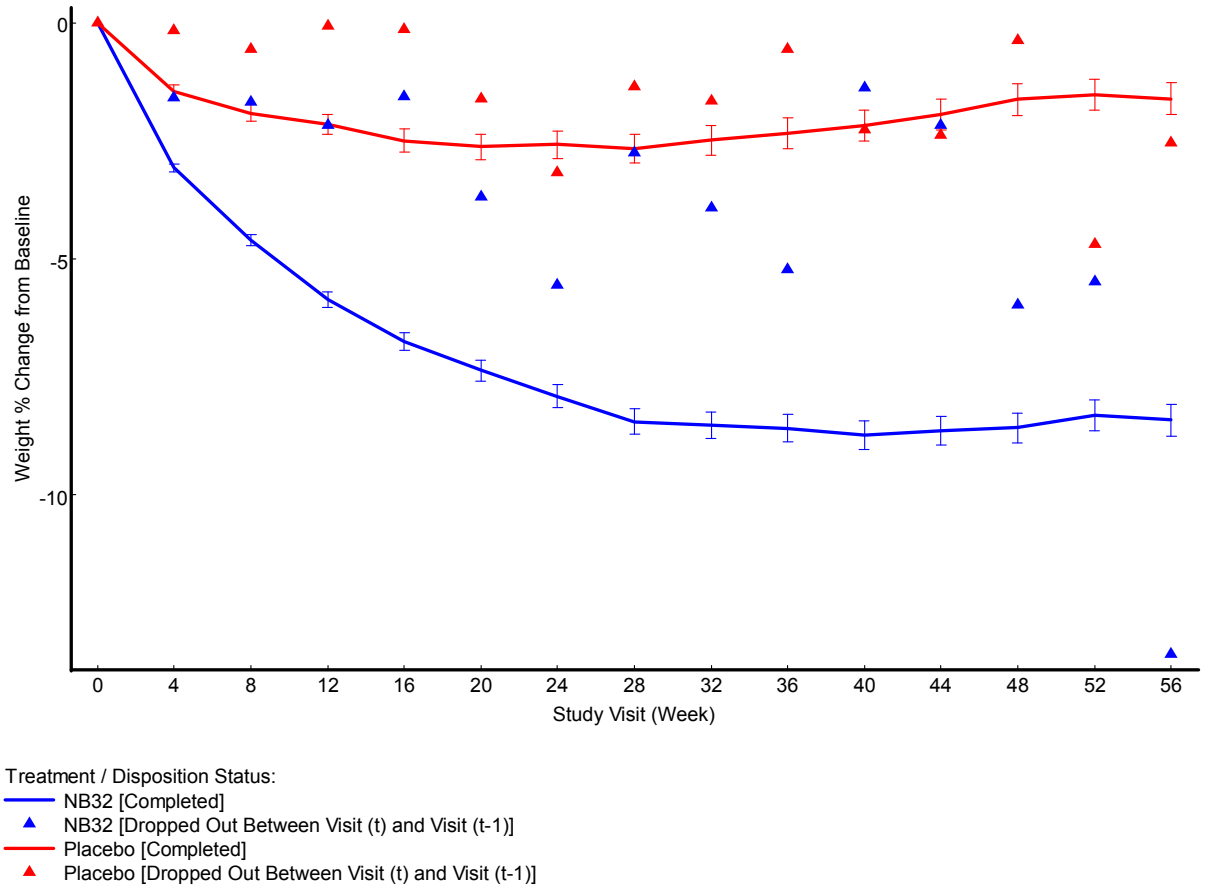


Notes:

- For subjects who stayed on study medication through week 56, the mean ± SEM is shown as a longitudinal profile. Subjects who completed study medication had treatment durations of 54-61 weeks in the efficacy database provided by the applicant (variable TRTDURWK).
- Single symbols represent the mean of subjects who discontinued in the time interval between the previous study visit (t-1) and the given study visit (t). Some subjects who were classified as "did not complete" study medications had treatment durations of 53-61 weeks: 7 in the NB32 arm, and 4 in the placebo group (variable TRTDURWK). This may represent errors in the efficacy database.
- The dose titration period was week 0 through week 4.

Source: Analysis by this reviewer

FIGURE 4 Study NB-303; For subjects who completed 56 weeks of study medication, mean weight change at each study visit. For subjects who discontinued, mean weight change at the study visit prior to discontinuation

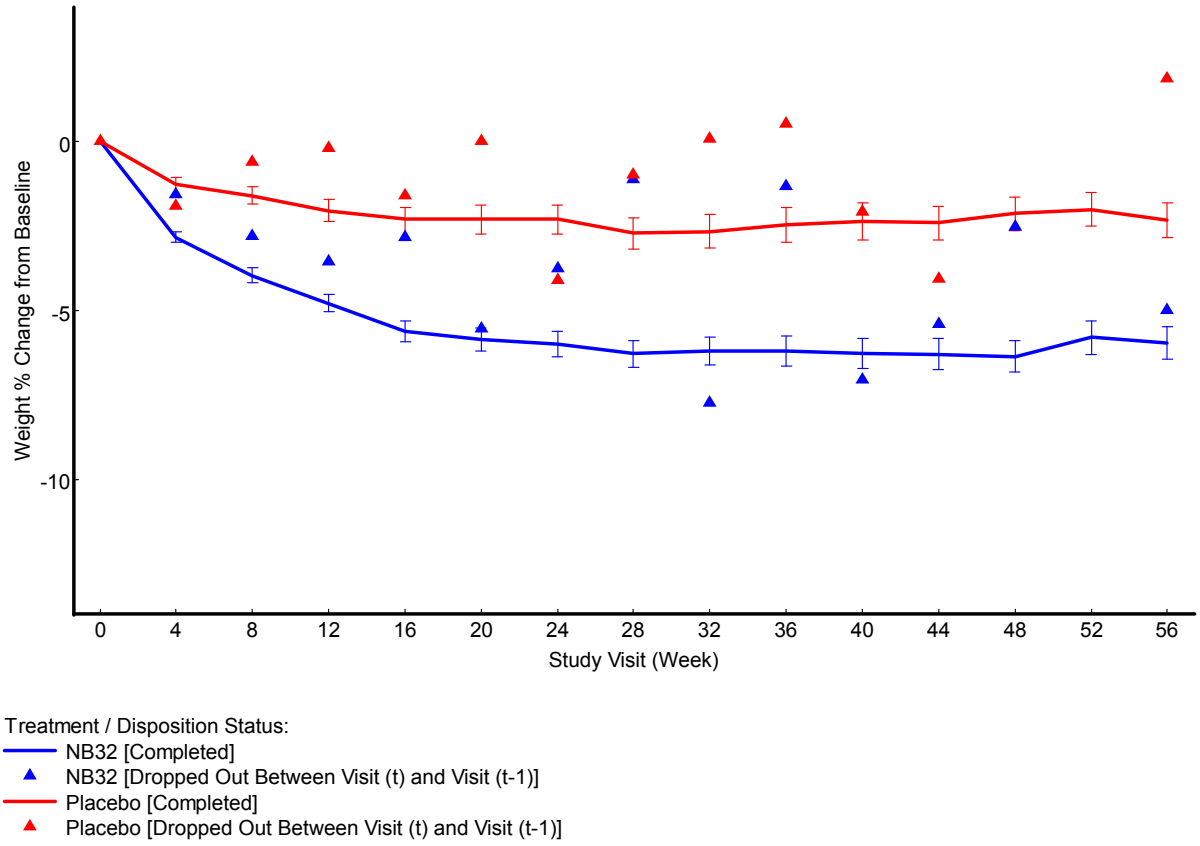


Notes:

- For subjects who stayed on study medication through week 56, the mean ± SEM is shown as a longitudinal profile. Subjects who completed study medication had treatment durations of 53-64 weeks in the efficacy database provided by the applicant (variable TRTDURWK).
- Single symbols represent the mean of subjects who discontinued in the time interval between the previous study visit (t-1) and the given study visit (t). A small number of subjects who were classified as "did not complete" study medications had treatment durations of 53-59 weeks: 7 in the NB32 arm, and 2 in the placebo group (variable TRTDURWK). This may represent errors in the efficacy database.
- Means include subjects in the NB32 arm who were re-randomized to receive NB48 in the re-randomization period starting at week 28 and continuing through week 44 (with the re-randomized dose continued through week 56).
- The dose titration period was week 0 through week 4.

Source: Analysis by this reviewer

FIGURE 5 Study NB-304; For subjects who completed 56 weeks of study medication, mean weight change at each study visit. For subjects who discontinued, mean weight change at the study visit prior to discontinuation



Notes:

- For subjects who stayed on study medication through week 56, the mean ± SEM is shown as a longitudinal profile. Subjects who completed study medication had treatment durations of 55-62 weeks in the efficacy database provided by the applicant (variable TRTDURWK).
- Single symbols represent the mean of subjects who discontinued in the time interval between the previous study visit (t-1) and the given study visit (t). A small number of subjects who were classified as "did not complete" study medications had treatment durations of 53-55 weeks: 2 in the NB32 arm, and 2 in the placebo group (variable TRTDURWK). This may represent errors in the efficacy database.
- The dose titration period was week 0 through week 4.

Source: Analysis by this reviewer

3.2. Subject demographic and baseline characteristics

Differences and similarities among the Phase 3 studies reflected the enrollment of subjects with type 2 diabetes in Study NB-304 and subjects who did not have type 2 diabetes in Studies NB-301, NB-302 and NB-303 (TABLE 6). The average age of diabetic subjects in Study NB-304 was greater than the average of subjects in the other three studies. Males and females were approximately equally represented among diabetic subjects in Study NB-304, whereas the large majority of subjects in the other three studies were female. A greater percentage of diabetic

subjects in Study NB-304 had hypertension, dyslipidemia, and/or metabolic syndrome at baseline than did the non-diabetic subjects in the other three studies. All four studies were relatively similar in the distribution of racial groups, with the large majority of subjects from the Caucasian racial group (TABLE 6). Average weight at baseline was also relatively similar at approximately 100 kg. A similar percentage, approximately 60%, of subjects had BMI ≥ 35 kg/m^2 at baseline in all four studies.

TABLE 6 Subject demographic and baseline characteristics in the randomized subjects in each of the four Phase 3 studies

	Study NB-301 n=1742	**Study NB-302 n=793**	**Study NB-303 n=1496**	**Study NB-304 n=505**
Age (years)				
Mean ± SD	44.1 ± 11.2	48.5 ± 10.7	44.3 ± 11.2	53.8 ± 9.3
Median	45.0	47	45.0	54.0
Range	18 to 66	19 to 65	18 to 65	20 to 72
≥ 65 years (n, %)	---	---	---	61 (12.1%)
Sex				
Male (n, %)	260 (14.9%)	80 (10.1%)	229 (15.3%)	220 (43.6)
Female (n, %)	1482 (85.1%)	713 (89.9%)	1267 (84.7%)	285 (56.4)
Race[1]				
Caucasian/ White	1307 (75.0%)	554 (69.9%)	1249 (83.5%)	401 (79.4%)
African American/ Black	338 (19.4%)	189 (23.8%)	205 (13.7%)	81 (16.0%)
Asian	14 (0.8%)	8 (1.0%)	16 (1.1%)	12 (2.4%)
Native Hawaiian / Pacific Islander	15 (0.9%)	1 (0.1%)	4 (0.3%)	1 (0.2%)
American Indian / Alaska Native	48 (2.8%)	8 (1.0%)	12 (0.8%)	4 (0.8%)
Other	20 (1.1%)	33 (4.2%)	10 (0.7%)	6 (1.2%)
Ethnicity[2]				
Hispanic/ Latino	229 (13.1%)	77 (9.7%)	114 (7.6%)	58 (11.5%)
Not Hispanic/ Latino	1513 (86.9%)	716 (90.3%)	1382 (92.4%)	447 (88.5%)
Weight (kg)				
Mean ± SD	99.6 ± 15.0	100.6 ± 15.3	100.0 ± 16.3	104.5 ± 18.3
Median	98	100.0	98.0	104.0
Range	62 to 155	66 to 162	66 to 168	64 to 167
BMI (kg/m^2)				
Mean ± SD	36.2 ± 4.2	36.5 ± 4.2	36.2 ± 4.4	36.4 ± 4.7
Median	36.0	36.0	36.0	36.0
Range	27.0 to 47.0	28.0 to 46.0	27.0 to 46.0	27.0 to 46.0
Obesity class (n, %)				
BMI < kg/m^2	39 (2.2%)	9 (1.1%)	39 (2.6%)	29 (5.7%)
BMI ≥ 30 and < 35	659 (37.8%)	271 (34.2%)	584 (39.0%)	160 (31.7%)
BMI ≥ 35 and < 40	633 (36.3%)	309 (39.0%)	507 (33.9%)	174 (34.5%)
BMI ≥ 40	411 (23.6%)	204 (25.7%)	366 (24.5%)	142 (28.1%)
Subgroups (n, %)				
Hypertension	315 (21.7%)	123 (15.5%)	318 (21.3%)	315 (62.4%)
Dyslipidemia	736 (50.7%)	351 (44.3%)	823 (55.0%)	425 (84.2%)

	Study NB-301 n=1742	Study NB-302 n=793	Study NB-303 n=1496	Study NB-304 n=505
Metabolic	388 (26.7%)	188 (23.7%)	450 (30.1%)	358 (70.9%)
Impaired fasting glucose	376 (25.9%)	177 (22.3%)	407 (27.2%)	---[1]
HbA1c > 8.0%	---[2]	---	---	181 (35.8%)
Sulfonylurea pharmacotherapy	---	---	---	241 (52.3%)

Notes:

[1] Impaired fasting glucose was not a subgroup for the diabetic population in Study NB-304

[2] HbA1c and Sulfonylurea pharmacotherapy did not define subgroups for the non-diabetic populations of Studies NB-301, NB-302 and NB-303.

Sources:

Tables ISE.301.1-3, ISE.301.1-5, ISE 302.1-3, ISE 302.1-5, ISE 303.1-3, ISE 303.1-5, ISE 304.1-3, ISE 304.1-5

3.3. Analysis populations

All four Phase 3 studies used the same definitions for the analysis populations, with exceptions as described below:

Full Analysis Set (FAS): The full analysis set included all subjects who were randomized, had a baseline body weight measurement, and at least one post-baseline body weight measurement while on study drug. Baseline was defined as the last non-missing measurement across all the visits before or at the time of randomization. Endpoint was defined as the last non-missing postbaseline measurement while on study drug (last observation carried forward, LOCF). Efficacy assessments that occurred within 1 day following the last dose date were considered valid.

Per Protocol Analysis Set (PP): The per protocol analysis set included all subjects in the FAS who received at least 28 weeks of study treatment, were "at least 70% compliant" with study medication.

Intent-to-Treat Analysis Set (ITT): The ITT analysis set included all randomized subjects with a baseline and postbaseline body weight, where endpoint was defined as the last non-missing postbaseline (LOCF_ITT) measurement during the double-blind treatment phase (irrespective of being on study drug at the time of the last measurement). A key difference between the FAS and the ITT set is that for the ITT analysis the efficacy assessments were considered valid even if they occurred while off study drug.

Completers Analysis Set: For studies NB-301, NB-303 and NB-304, the completers analysis set included all randomized subjects with a baseline measurement, a postbaseline body weight measurement, and who completed 56 weeks of treatment. For Study NB-302, the completers analysis set included all randomized subjects with a baseline measurement and a post-baseline measurement at week 56 while on study drug (i.e., active treatment). The interpretation of this difference is still under review, as is a difference in the number of completers per arm in Study NB-202 as classified by disposition status (TABLE 5) and as classified by the analysis set (TABLE 10, TABLE 11). For Study NB-303, an additional completers analysis set was defined for week 28.

Safety Analysis Set: The safety analysis set for analysis during the double blind treatment phase included all randomized subjects who were administered at least one tablet of study treatment and had at least one investigator context / assessment at any time after the start of study treatment, regardless of whether or not they discontinued the study.

TABLE 7 Analysis populations defined for Studies NB-301, NB-302, NB-303 and NB-304

Analysis set, n (%)	Study NB-301			StudyNB-302	
	NB-16	NB-32	Placebo	NB-32	Placebo
Number randomized	578	583	581	591	202
Safety Analysis Set	569 (98.4)	573 (98.3)	569 (97.9)	584 (98.8)	200 (99.0)
Efficacy Analysis Sets					
Intention-to-Treat Set	524 (90.7)	538 (90.7)	536 (92.3)	note 1	
Full Analysis Set	471 (81.5)	471 (80.8)	511 (88.0)	482 (81.6)	193 (95.5)
Per Protocol Set	263 (45.5)	267 (45.5)	251 (43.2)	245 (41.5)	92 (45.5)
Completers Analysis Set, Week 56	284 (49.1)	296 (50.8)	290 (49.9)	301 (50.9)	106 (52.5)

	Study NB-303		Study NB-304	
	NB-32	Placebo	NB-32	Placebo
Number randomized	1001	495	335	170
Safety Analysis Sets	992 (99.1)	492 (99.4)	333 (99.4)	169 (99.4)
Efficacy Analysis Sets				
Intention-to-Treat Set	943 (94.2)	474 (95.8)	321 (95.8)	166 (97.6)
Full Analysis Set	825 (82.4)	456 (92.1)	265 (79.1)	159 (93.5)
Per Protocol Set	483 (48.3)	248 (50.1)	149 (44.5)	102 (60.0)
Completers Analysis Set, Week 56	538 (53.7)	267 (53.9)	175 (52.2)	100 (58.8)
Completers Analysis Set, Week 28[2]	619 (61.8)	319 (64.4)	note 3	

Notes
[1] Study NB-302 did not define an intention-to-treat set
[2] Study NB-303 defined a completers analysis set for week 28

Sources: Study NB301 report, Table 6; Study NB302 report, Table 4; Study NB303 report, Table 4; Study NB304 report, Table 5

3.4. Primary efficacy endpoint

For Study NB-301, NB-302 and NB-304, the applicant defined two co-primary efficacy endpoints: (1) the proportion of subjects achieving ≥ 5% reduction in body weight at the end of 56 weeks of treatment and (2) the change from baseline to the end of week 56. These are the co-primary endpoints that are described in the weight management guidance.

Study NB-303 evaluated these endpoints at the end of week 28 as the primary endpoint. This was in response to recommendations from the biometrics review team and the medical division (see letters dated June 9, 2009 and June 23, 2009, submitted under IND 068858). The reason for this recommendation was the differential treatment of subjects randomized to the NB32 arm and the placebo arm after week 28, as described in the 6/9/09 letter:

> The reason for our disagreement is the differential treatment of the two randomized study arms which begins at week 28 with the re-randomization protocol and continues through week 44. We believe that this differential treatment of the two study arms is likely to introduce bias into the estimate of the efficacy of the efficacy of the naltrexone 36 mg / bupropion 360 mg/day (nal36/bup) at week 56. The estimated placebo-adjusted weight loss attributed to nal36/bup may tend to be larger than it actually is in the target population.
>
> The re-randomization of subjects who have not lost at least 5% of baseline body weight by week 28 initiates a differential treatment of subjects depending on their randomized assignment. A subject in the placebo arm continues on the placebo. A subject in the nal32/bup360 arm is re-randomized, with a 50% chance of being assigned to a higher dose, naltrexone 48 mg/bupropion 360 mg/day (nal48/bup360), and a 50% chance of staying with the nal32/bup360. This re-randomization protocol continues for weeks 32 through 44. This means that a subject who has not yet been assigned to the nal48/bup360 dose may be re-evaluated every 4 weeks from week 28 through week 44, with the possibility of re-randomization to the nal48/bup360 dose at each evaluation, conditional on having been randomized to the nal32/bup360 arm and having not lost at least 5% of baseline body weight.
>
> We believe that the re-randomization protocol is likely to result in a biased overestimate of the efficacy of the nal32/bup360 dose in comparison with the placebo. The basis for this belief is the assumption that subjects in the nal32/bup360 arm who do not lose at least 5% of baseline body weight by week 28 may be non-responders to this dose. They may be similar to patients treated by placebo with regard to the trend in body weight from week 28 to week 56. The potential for a biased overestimate is caused by (1) using the last observation carried forward (LOCF) at the point of assignment to the nal48/bup360 dose for subjects in this subgroup who are in the nal32/bup360 arm, while (2) continuing to include weight records for subjects in this subgroup who are in the placebo arm.
>
> These reasons support our recommendation to use week 28 as the primary efficacy endpoint period. Results at week 56 can be used in supportive analyses.

Based on the 2007 weight management guidance, the efficacy of Contrave would be supported if either one or both the co-primary endpoints were statistically significant (see Part IV-B-3-c). However, the ICH-E9 guidance advises that in the event that a protocol identifies more than one primary endpoint, "the effect on the Type I error should be explained because of the potential for multiplicity problems …; the method of controlling Type I error should be given in the protocol."[5] This places the weight management guidance at variance with the recommendation

[5] Part II.B.5., *Guidance for Industry, E9 Statistical Principles for Clinical Trials*, September 1998

from the ICH-E9 guidance. The inferential tests for each co-primary endpoint between an active treatment arm and placebo were assessed against a two-sided significance level of 0.05 separately. The protocols state that the tests conducted for each endpoint "must be significant versus the two-sided significance level of 0.05 (i.e. both p-values < 0.05)." This statement can be interpreted to mean that the efficacy of Contrave would be supported only if both co-primary endpoints were significant.

3.5. Statistical analysis methods for primary efficacy endpoint

Primary analysis model: The primary analysis was performed for the FAS analysis set, using last non-missing observation carried forward (LOCF). For percent change from baseline, an analysis of covariance (ANCOVA) model included treatment group and study center as the main effects with baseline measurement as the covariate. The primary analysis for the percentage of subjects achieving ≥ 5% weight loss from baseline was based on a linear logistic regression model, using treatment group and study center as the main effects with the baseline measurement as the covariate. The biostatistics review team concurred with the analysis plan (see letter dated June 9, 2009).

Sensitivity analyses of the co-primary endpoints: In my opinion, the applicant used a reasonable set of analyses that explored the effect of different analysis sets and analysis models on the study conclusions. The sensitivity analysis included plausible interpretations of the weight response of subjects who discontinued. As I discussed in part 3.1 of this review, subjects who withdrew from study medication early had lost less weight at the time of withdrawal, compared to the average weight loss at the same study visit in subjects who completed 56 weeks of study medication. The sensitivity analysis included the following approaches:

a) The primary analysis model with different analysis sets, for both co-primary endpoints. These analysis sets included the ITT analysis set, the completers set and the per protocol set.

b) A repeated measures linear mixed-effects model for the continuous endpoint. This analysis used the ITT analysis set with no estimation for missing data. The analysis model had a random subject effect, fixed class effects for treatment, time (i.e., week), study center, the treatment-by-time interaction, with baseline as a covariate. The Kenward-Rogers approximation was used to estimate the denominator degrees of freedom.

c) A weight regain imputation method, for both co-primary endpoints. The primary analysis model was used, for all randomized subjects, but with an estimate of weight at week 56 in subjects who discontinued early, based on a rate of 0.3 kg of regained weight per month[6]. The estimate was bounded by the subject's baseline weight. If a subject did not return after enrollment (i.e., the subject had no post-baseline weights), the baseline was imputed for all missing values.

[6] See Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD et al, 2009. Comparison of weight-loss diets with different compositions of fat, protein and carbohydrates. NEJM 360:859-873.

d) A baseline carried forward imputation method, for both co-primary endpoints. For all randomized subjects, the endpoint was defined as the week 56 measurement, irrespective of being on study drug or not. For randomized subjects who discontinued active study drug prior to week 56, the endpoint was the baseline measurement (i.e., the percent change from baseline was equal to zero for these subjects). For all subjects who discontinued active study drug prior to week 56, the baseline weight was used to estimate percent change from baseline. This means that subjects who discontinued study drug were estimated to have 0% change from baseline. This imputation was applied to all randomized subjects. The primary analysis models were used with this imputation method. The baseline carried forward method was applied to week 28 for the primary analysis of Study NB-303.

Adjustment for multiplicity with more than one NB dose: Study NB-301, which had two dose levels of Contrave, conducted the inferential tests associated with the co-primary comparisons in a stepwise manner beginning with the higher active treatment group. The inferential tests for each co-primary endpoint between an active treatment arm and placebo will be assessed against a two-sided significance of 0.05 separately. That is, the comparisons for each co-primary endpoint were each tested at a significance level of 0.05 for N32 vs. placebo only. If each endpoint was significant, $p<0.01$) for this treatment comparison, then the comparison for NB15 was conducted for each co-primary endpoint at a significance level of 0.05.

3.6. Results of the statistical analysis of efficacy

Continuous endpoint: After 56 weeks of treatment with naltrexone 32 mg / bupropion 360 mg subjects lost a statistically significant amount of weight. The primary endpoint was evaluated at 56 weeks for Study NB-301, NB-302 and NB-304, and at 28 weeks for Study NB-303. The placebo-adjusted mean effect of NB32 was somewhat less than 5%, the benchmark for clinical significance, but the 95% confidence intervals include 5% (TABLE 8, TABLE 10, TABLE 12, TABLE 14).

The majority of subjects who dropped out prior to the end of each study remained within ± 5% of their baseline body weight (FIGURE 6 - FIGURE 9, top portion of each bar). These are the subjects whose final weight was estimated by LOCF in the primary analysis.

Results from sensitivity analyses, including alternative analysis models and different analysis populations, supported the conclusion of the efficacy of NB32 in the continuous endpoint. Results were generally statistically significant, with placebo-adjusted mean effect somewhat less than 5%, and with a 95% CI including 5% (TABLE 8, TABLE 10, TABLE 12, TABLE 14). The placebo-adjusted mean effect of NB32 was generally greater in the completers and per protocol analysis sets than in the baseline-carried-forward and weight-regain analysis sets, as would be expected.

A summary of the results for the continuous weight loss endpoint in each study is as follows:

- Study NB-301 included two dose levels of the combination product NB32 and NB16. The average amount of weight lost in the NB32 arm was greater than the average weight loss in

the NB16 arm (TABLE 8). This result supports a dose-response relationship between these two dosages.

- Study NB-302 was conducted with an intensive program for behavior modification in both arms. The effectiveness of this program is demonstrated by the larger mean change from baseline in both the NB32 and placebo arms, compared with Study NB-301 (TABLE 10). However, the placebo-adjusted effect of NB32 in Study NB-302 is somewhat smaller than the effect in Study NB-301. This finding is consistent across the primary analysis and supportive analyses. Subjects in the placebo group of NB-302, with the intensive behavior modification program, may have been more successful in losing weight than subjects in the placebo group of NB-301.

- Study NB-303 evaluated the primary endpoint at week 28. However, the effect of NB28 at week 28 may be fairly similar to the effect at week 56. The longitudinal profile of mean weight loss in completers appears to stabilize at week 28 in all four studies (FIGURE 2 - FIGURE 5).

- Study NB-304 was conducted in obese subjects with type 2 diabetes. The placebo-adjusted effect of NB32 at week 56 was smaller than the effect in the other three studies (TABLE 14). This finding is consistent with the clinical expectation for less weight loss in diabetic subjects compared with non-diabetic subjects.

Categorical endpoint: After one year of treatment with NB32 (or 28 weeks in the case of Study NB-303), a statistically significantly greater percentage lost at least 5% of their baseline body weight, compared to placebo (TABLE 9, TABLE 11, TABLE 13, TABLE 15). The results from the analysis of the FAS were supported by the results from sensitivity analyses using other versions of the analysis data sets. This result supports the criterion for statistical significance in the 5% responder endpoint, as described in the weight management guidance.

Of the several sensitivity analyses, the analysis using the baseline observation carried forward (BOCF) may be of greatest interest. This is because: (1) the BOCF analysis can be applied to all randomized subjects; and (2) it may be reasonable to assume that most subjects who drop out of a weight loss study can be classified as non-responders. However, subjects also dropped out of the NB studies who were 5% responders at the time of dropout. For example, in Study NB-301, 226/471 (48%) of NB32 subjects were responders in the FAS/LOCF analysis set, while 180/583 (32%) were responders in the BOCF analysis set. The differences reflect 112 subjects who were randomized but were not in the FAS (having dropped out before providing any post-baseline weights), and 46 subjects who were responders at the time they dropped out. A similar finding occurs in the other 3 studies as well. Some subjects in the NB32 arm dropped out late in a study as responders (see the later weeks in FIGURE 2 - FIGURE 4). One interpretation of this pattern is that late dropout-responders in the NB32 arm were satisfied with their weight loss and no longer willing to tolerate the adverse events associated with NB32.

TABLE 8 Study NB-301; Body weight (kg), percent change from baseline to week 56 endpoint; Primary analysis and sensitivity analyses

Study NB-301: Customary diet and behavioral counseling	Group	n	Baseline mean (SD)	Percent Change from Baseline LSMean (SE)	LS Mean Difference from Placebo (95% CI)	p
1A. Full Analysis Set (LOCF): reported by applicant	Placebo	511	99.3 (14.3)	-1.3 (0.3)		
	NB16	471	100.1 (14.4)	-5.9 (0.3)	-3.7 (-4.5, -2.9)	<0.001
	NB32	471	100.2 (16.3)	-6.1 (0.3)	-4.8 (-5.6, -4.0)	<0.001
1B. Full Analysis Set (LOCF): this reviewer's analysis	Placebo	511	99.3 (14.3)	-1.4 (0.3)		
	NB16	471	100.1 (14.4)	-4.9 (0.3)	-3.5 (-4.3, -2.7)	<0.001
	NB32	471	100.2 (16.3)	-6.0 (0.3)	-4.6 (-5.4, -3.8)	<0.001
2. Completers Analysis Set	Placebo	290	99.2 (14.6)	-1.8 (0.5)		
	NB16	284	99.8 (14.6)	-6.7 (0.5)	-4.9 (-6.1, -3.6)	<0.001
	NB32	296	99.8 (16.4)	-8.1 (0.5)	-6.2 (-7.5, -5.0)	<0.001
3. ITT Analysis Set	Placebo	536	99.5 (14.4)	-1.3 (0.3)		
	NB16	524	99.5 (14.5)	-4.5 (0.3)	-3.2 (-4.0, -2.4)	<0.001
	NB32	538	99.8 (16.1)	-5.4 (0.3)	-4.1 (-4.9, -3.3)	<0.001
4. Weight Regain Imputation Method	Placebo	581	99.5 (14.3)	-1.2 (0.3)		
	NB16	578	99.5 (14.8)	-3.7 (0.3)	-2.5 (-3.2, -1.8)	<0.001
	NB32	583	99.7 (14.8)	-4.6 (0.3)	-3.4 (-4.1, -2.7)	<0.001
5. Baseline Carried Forward Analysis	Placebo	581	99.5 (14.3)	-0.9 (0.3)		
	NB16	578	99.5 (14.3)	-3.3 (0.3)	-2.4 (-3.1, -1.7)	<0.001
	NB32	583	99.7 (15.9)	-4.0 (0.3)	-3.1 (-3.8, -2.4)	<0.001
6. Mixed Model Repeated Measures (FAS)	Placebo	511	99.2 (14.5)	-1.0 (0.4)		
	NB16	471	99.5 (14.4)	-5.2 (0.4)	-4.3 (-5.3, -3.2)	<0.001
	NB32	471	99.9 (16.3)	-6.6 (0.4)	-5.7 (-6.7, -4.6)	<0.001
7. Per Protocol Set	Placebo	251	99.3 (14.9)	-2.3 (0.5)		
	NB16	262	100.6 (14.9)	-7.1 (0.5)	-4.7 (-6.1, -3.4)	<0.001
	NB32	267	100.3 (17.0)	-8.3 (0.5)	-6.0 (-7.3, -4.6)	<0.001

Source: Table ISE.301.1-6, Table 14.2-5

TABLE 9 Study NB-301; Body weight, proportion 5% responders at week 56; primary analysis and sensitivity analyses.

Study NB-301: Customary diet and behavioral counseling	Group	n	5% responders n(%)	Odds Ratio (vs. placebo)	95% CI of Odds Ratio	p
1A. Full Analysis Set (LOCF)	Placebo	511	84 (16.4%)			
	NB16	471	186 (39.5%)	3.4	(2.5, 4.6)	<0.001
	NB32	471	226 (48.0%)	4.9	(3.6, 6.6)	<0.001
1B. Full Analysis Set (LOCF): this reviewer's analysis	Placebo	511	84 (16.4%)			
	NB16	471	186 (39.5%)	3.4	(2.5, 4.6)	<0.001
	NB32	471	226 (48.0%)	4.9	(3.6, 6.6)	<0.001
2. Completers Analysis Set	Placebo	290	67 (23.1%)			
	NB16	284	155 (54.6%)	4.2	(2.9, 6.1)	<0.001
	NB32	296	183 (61.8%)	5.8	(4.0, 8.3)	<0.001
3. ITT Analysis Set	Placebo	536	93 (17.4%)			
	NB16	524	190 (36.3%)	2.8	(2.1, 3.7)	<0.001
	NB32	538	226 (42.0%)	3.6	(2.7, 4.8)	<0.001
4. Weight Regain Imputation Method	Placebo	581	78 (13.4%)			
	NB16	578	175 (30.3%)	2.9	(2.1, 3.9)	<0.001
	NB32	583	203 (34.8%)	3.6	(2.7, 4.9)	<0.001
5. Baseline Carried Forward Analysis	Placebo	581	67 (11.5%)			
	NB16	578	156 (27.0%)	2.9	(2.1, 4.0)	<0.001
	NB32	583	180 (30.9%)	3.6	(2.6, 4.9)	<0.001
6. Per Protocol Set	Placebo	251	67 (26.7%)			
	NB16	263	141 (52.6%)	3.4	(2.3, 5.0)	<0.001
	NB32	267	162 (60.7%)	4.6	(3.1, 6.8)	<0.001

Source: Table ISE.301.1-7, Table 14.2-20

TABLE 10 Study NB-302; Body weight (kg), percent change from baseline to week 56 endpoint; Primary analysis and sensitivity analyses

Study NB-302: Intensive program for behavior modification	Group	n	Baseline mean (SD)	Percent Change from Baseline LSMean (SE)	LS Mean Difference from Placebo (95% CI)	p
1. Full Analysis Set (LOCF)[1]	Placebo	193	101.9 (15.0)	-5.1 (0.6)		
	NB32	482	100.7 (15.4)	-9.3 (0.4)	-4.2 (-5.6, -2.9)	<0.001
2. Completers Analysis Set	Placebo	106	100.4 (14.3)	-7.3 (0.9)		
	NB32	301	101.2 (15.1)	-11.5 (0.6)	-4.2 (-6.1, -2.4)	<0.001
3. ITT Analysis Set	Placebo	196	101.8 (15.0)	-4.9 (0.6)		
	NB32	565	100.3 (15.5)	-8.1 (0.4)	-3.2 (-4.5, -1.8)	<0.001
4. Weight Regain Imputation Method	Placebo	202	101.9 (15.0)	-4.9 (0.6)		
	NB32	591	100.2 (15.4)	-7.3 (0.4)	-2.4 (-3.7, -1.1)	<0.001
5. Baseline Carried Forward Analysis	Placebo	202	101.9 (15.0)	-4.2 (0.6)		
	NB32	591	100.2 (15.4)	-6.4 (0.4)	-2.2 (-3.5, -0.9)	<0.001
6. Mixed Model Repeated Measures (FAS)	Placebo	193	100.4 (14.3)	-5.4 (0.7)		
	NB32	482	101.2 (15.1)	-10.3 (0.4)	-5.0 (-6.6, -3.3)	<0.001
7. Per Protocol	Placebo	92	101.3 (14.7)	-8.0 (1.0)		
	NB32	245	99.3 (14.6)	-12.0 (0.7)	-4.0 (-6.1, -1.9)	<0.001

Note 1: I confirmed the results for the FAS.

Source: Table ISE.302.1-6, Table 14.2-5

TABLE 11 Study NB-302; Body weight, proportion 5% responders at week 56; primary analysis and sensitivity analyses.

Study NB-302: Intensive program for behavior modification	Group	n	5% responders n(%)	Odds Ratio (vs. placebo)	95% CI of Odds Ratio	p
1. Full Analysis Set (LOCF) [1]	Placebo	193	82 (42.5%)			
	NB32	482	320 (66.4%)	2.8	(2.0, 4.1)	<0.001
2. Completers Analysis Set	Placebo	106	64 (60.4%)			
	NB32	301	242 (80.4%)	2.9	(1.8, 4.8)	<0.001
3. ITT Analysis Set	Placebo	196	84 (42.9%)			
	NB32	565	321 (56.8%)	1.8	(1.3, 2.6)	<0.001
4. Weight Regain Imputation Method	Placebo	202	77 (38.1%)			
	NB32	591	304 (51.4%)	1.8	(1.3, 2.5)	<0.001
5. Baseline Carried Forward Analysis	Placebo	202	68 (33.7%)			
	NB32	591	269 (45.5%)	1.7	(1.2, 2.4)	<0.001
6. Per Protocol Set	Placebo	92	57 (62.0%)			
	NB32	145	198 (80.8%)	3.0	(1.7, 5.2)	<0.001

Note 1: I confirmed the results for the FAS.

Source: Table ISE.302.1-7, Table 14.2-19

TABLE 12 Study NB-303; Body weight (kg), percent change from baseline to week 28 endpoint; Primary analysis and sensitivity analyses

Study NB-303: Customary diet and behavioral counseling	Group	n	Baseline mean (SD)	Percent Change from Baseline LSMean (SE)	LS Mean Difference from Placebo (95% CI)	p
1. Full Analysis Set (LOCF) [1]	Placebo	456	99.3 (16.0)	-1.9 (0.3)		
	NB32	825	100.7 (16.7)	-6.5 (0.2)	-4.6 (-5.2, -3.9)	<0.001
2. Completers Analysis Set	Placebo	319	99.0 (15.99)	-2.4 (0.3)		
	NB32	619	101.2 (17.1)	-7.8 (0.2)	-5.4 (-6.2, -4.6)	<0.001
3. ITT Analysis Set	Placebo	474	99.4 (15.9)	-1.9 (0.3)		
	NB32	943	100.4 (16.7)	-5.7 (0.2)	-3.9 (-4.5, -3.2)	<0.001
4. Weight Regain Imputation Method	Placebo	495	99.2 (15.9)	-1.9 (0.3)		
	NB32	1001	100.3(16.6)	-5.2 (0.2)	-3.4 (-3.9, -2.8)	<0.001
5. Baseline Carried Forward Analysis	Placebo	495	99.2(15.9)	-1.5 (0.3)		
	NB32	1001	100.3 (16.6)	-4.8 (0.2)	-3.3 (-3.9, -2.7)	<0.001
6. Mixed Model Repeated Measures (FAS)	Placebo	456	99.1 (15.9)	-2.1 (0.3)		
	NB32	825	101.0 (17.0)	-7.2 (0.2)	-5.1 (-5.8, -4.4)	<0.001
7. Per Protocol Set	Placebo	248	98.5 (15.9)	-2.8 (0.4)		
	NB32	483	101.2 (17.2)	-8.2 (0.3)	-5.4 (-6.3, -4.5)	<0.001

Note 1: I confirmed the results for the FAS.

Source: Table ISE.303.1-6A, Table 14.2-9

TABLE 13 Study NB-303 at week 28; Body weight, proportion 5% responders at week 28; primary analysis and sensitivity analyses.

Study NB-303: Customary diet and behavioral counseling	Group	n	5% responders n(%)	Odds Ratio (vs. placebo)	95% CI of Odds Ratio	p
1. Full Analysis Set (LOCF) [1]	Placebo	456	80 (17.5%)			
	NB32	825	459 (55.6%)	6.6	(5.0, 8.8)	<0.001
2. Completers Analysis Set	Placebo	319	71 (22.3%)			
	NB32	619	426 (68.8%)	8.7	(6.2, 12.1)	<0.001
3. ITT Analysis Set	Placebo	474	81 (17.1%)			
	NB32	943	461 (48.9%)	5.1	(3.9, 6.8)	<0.001
4. Weight Regain Imputation Method	Placebo	495	79 (16.0%)			
	NB32	1001	446 (44.6%)	4.7	(3.5, 6.2)	<0.001
5. Baseline Carried Forward Analysis	Placebo	495	69 (13.9%)			
	NB32	1001	421 (42.1%)	4.9	(3.7, 6.6)	<0.001
6. Per Protocol Set	Placebo	248	64 (25.8%)			
	NB32	483	345 (71.4%)	8.4	(5.7, 12.2)	<0.001

Note 1: I confirmed the results for the FAS.

Source: Table ISE.303.1-7A, Table 14.2-37

TABLE 14 Study NB-304; Body weight (kg), percent change from baseline to week 56 endpoint; Primary analysis and sensitivity analyses

Study NB-304: Obese subjects with type 2 diabetes	Group	n	Baseline mean (SD)	Percent Change from Baseline LSMean (SE)	LS Mean Difference from Placebo (95% CI)	p
1A. Full Analysis Set (LOCF)	Placebo	159	105.0 (17.1)	-1.8 (0.4)		
	NB32	265	106.5 (19.1)	-5.0 (0.3)	-3.3 (-4.3, -2.2)	<0.001
1B. Full Analysis Set (LOCF): this reviewer's analysis	Placebo	159	105.0 (17.1)	-2.1 (0.5)		
	NB32	265	106.4 (19.1)	-5.5 (0.4)	-3.4 (-4.5, -2.3)	<0.001
2. Completers Analysis Set	Placebo	100	105.1 (16.9)	-2.2 (0.6)		
	NB32	175	107.0 (19.5)	-5.9 (0.5)	-3.7 (-5.2, -2.2)	<0.001
3. ITT Analysis Set	Placebo	166	105.3 (16.9)	-1.7 (0.4)		
	NB32	321	104.2 (19.1)	-3.7 (0.3)	-2.0 (-3.0, -1.0)	<0.001
4. Weight Regain Imputation Method	Placebo	170	105.1 (17.0)	-1.7 (0.4)		
	NB32	335	104.2 (18.9)	-3.5 (0.3)	-1.9 (-2.8, -0.9)	<0.001
5. Baseline Carried Forward Analysis	Placebo	170	105.1 (17.0)	-1.3 (0.4)		
	NB32	335	104.2 (18.9)	-3.1 (0.3)	-1.7 (-2.7, -0.8)	<0.001
6. Mixed Model Repeated Measures (FAS)	Placebo	159	105.3 (17.1)	-1.9 (0.5)		
	NB32	265	107.1 (19.3)	-5.6 (0.4)	-3.7 (-5.0, -2.4)	<0.001
7. Per Protocol Set	Placebo	102	104.4 (17.4)	-2.0 (0.6)		
	NB32	149	107.7 (20.1)	-6.1 (0.5)	-4.2 (-5.7, -2.6)	<0.001

Source: Table ISE.304.1-6, Table 14.2-5

TABLE 15 Study NB-304; Body weight, proportion 5% responders at week 56; primary analysis and sensitivity analyses.

Study NB-304: Obese subjects with type 2 diabetes	Group	n	5% responders n(%)	Odds Ratio (vs. placebo)	95% CI of Odds Ratio	p
Full Analysis Set (LOCF) [1]	Placebo	159	30 (18.9%)			
	NB32	265	118 (44.5%)	3.4	(2.2, 5.5)	<0.001
Completers Analysis Set	Placebo	100	24 (24.0%)			
	NB32	175	93 (53.1%)	3.7	(2.1, 6.5)	<0.001
ITT Analysis Set	Placebo	166	30 (18.1%)			
	NB32	321	115 (35.8%)	2.5	(1.6, 4.0)	<0.001
Weight Regain Imputation Method	Placebo	170	27 (15.9%)			
	NB32	335	104 (31.0%)	2.4	(1.5, 3.8)	<0.001
Baseline Carried Forward Analysis	Placebo	170	24 (14.1%)			
	NB32	335	94 (28.1%)	2.4	(1.4, 3.9)	<0.001
Per Protocol Set	Placebo	102	25 (24.5%)			
	NB32	149	82 (55.0%)	4.0	(2.3, 7.1)	<0.001

Note 1: I confirmed the results for the FAS, after removing the term "site" from the model (based on problems with model validity with the term "site" included).

Source: Table ISE.304.1-7, Table 14.2-22

FIGURE 6 Study NB-301; Distribution of weight change at week 52; FAS analysis set

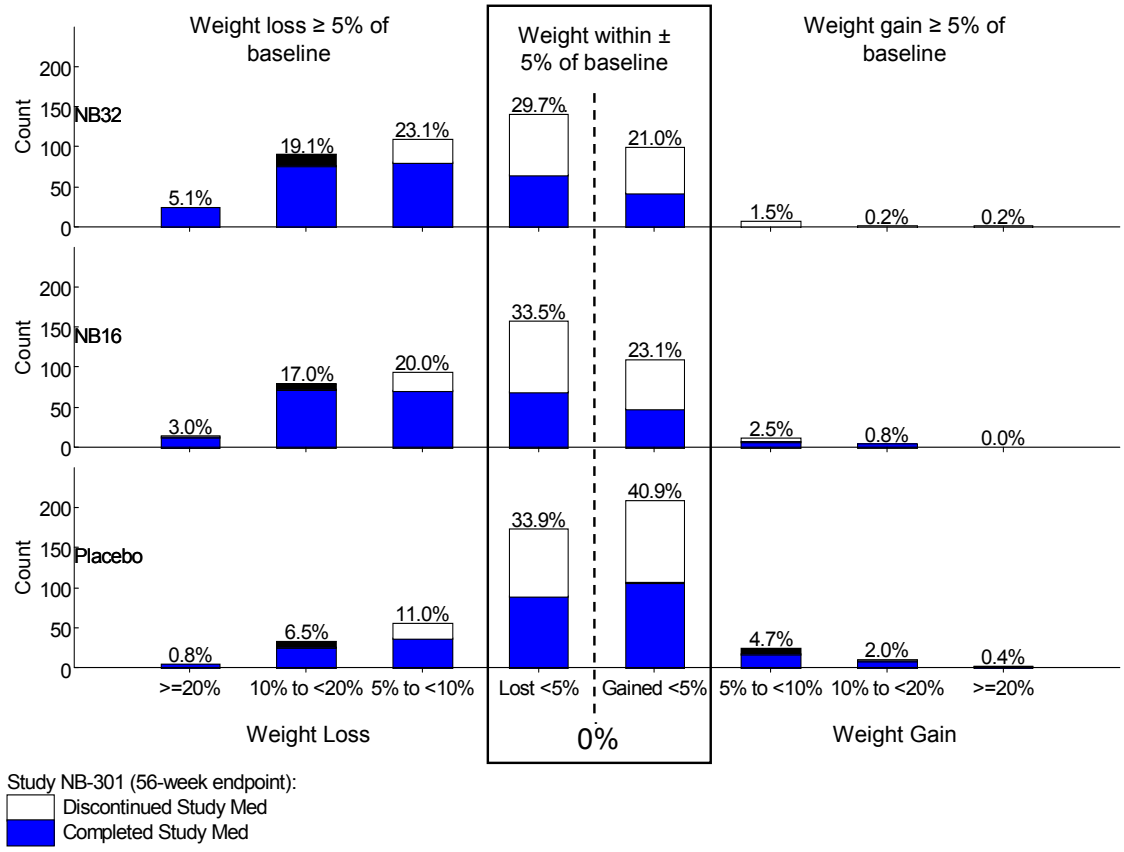


FIGURE 7 Study NB-302; Distribution of weight change at week 56; FAS analysis set

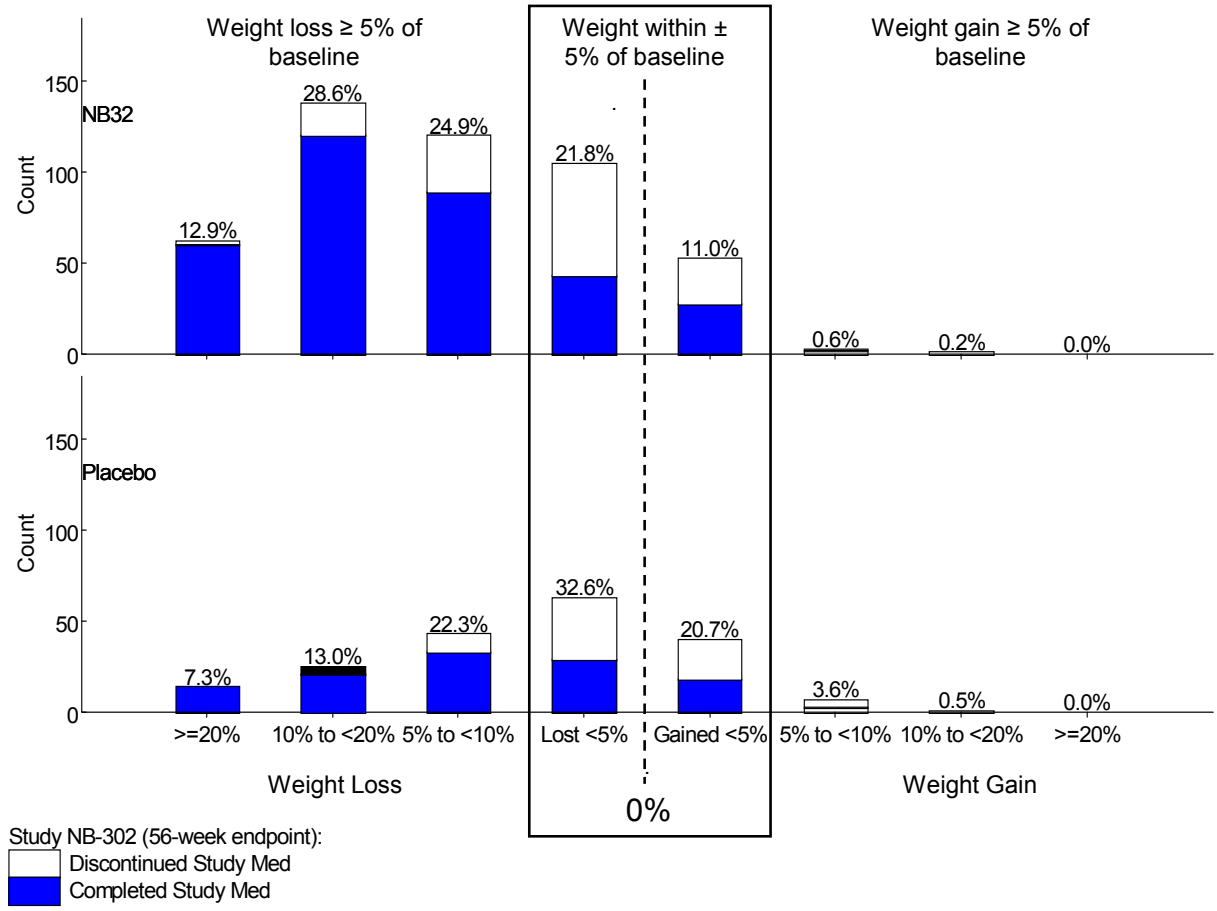


FIGURE 8 Study NB-303; Distribution of weight change at week 28; FAS analysis set

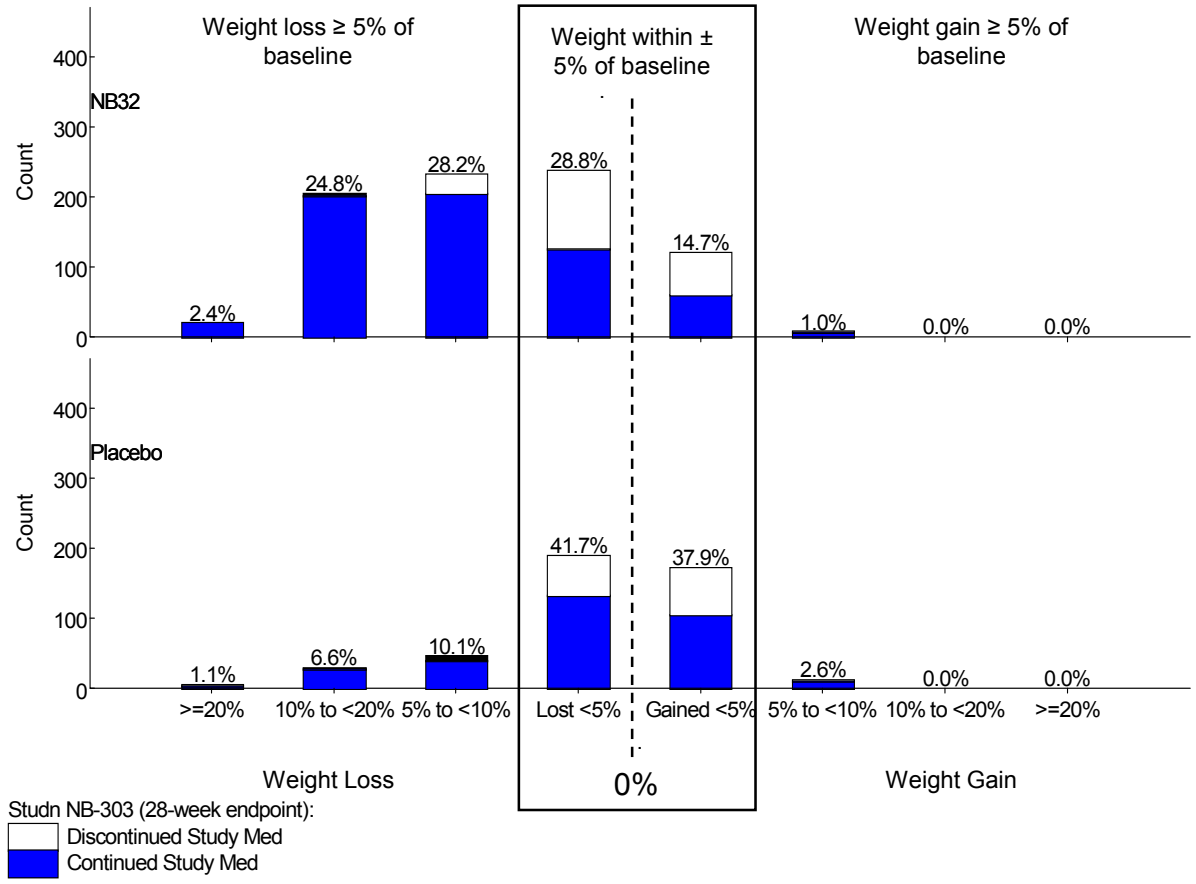
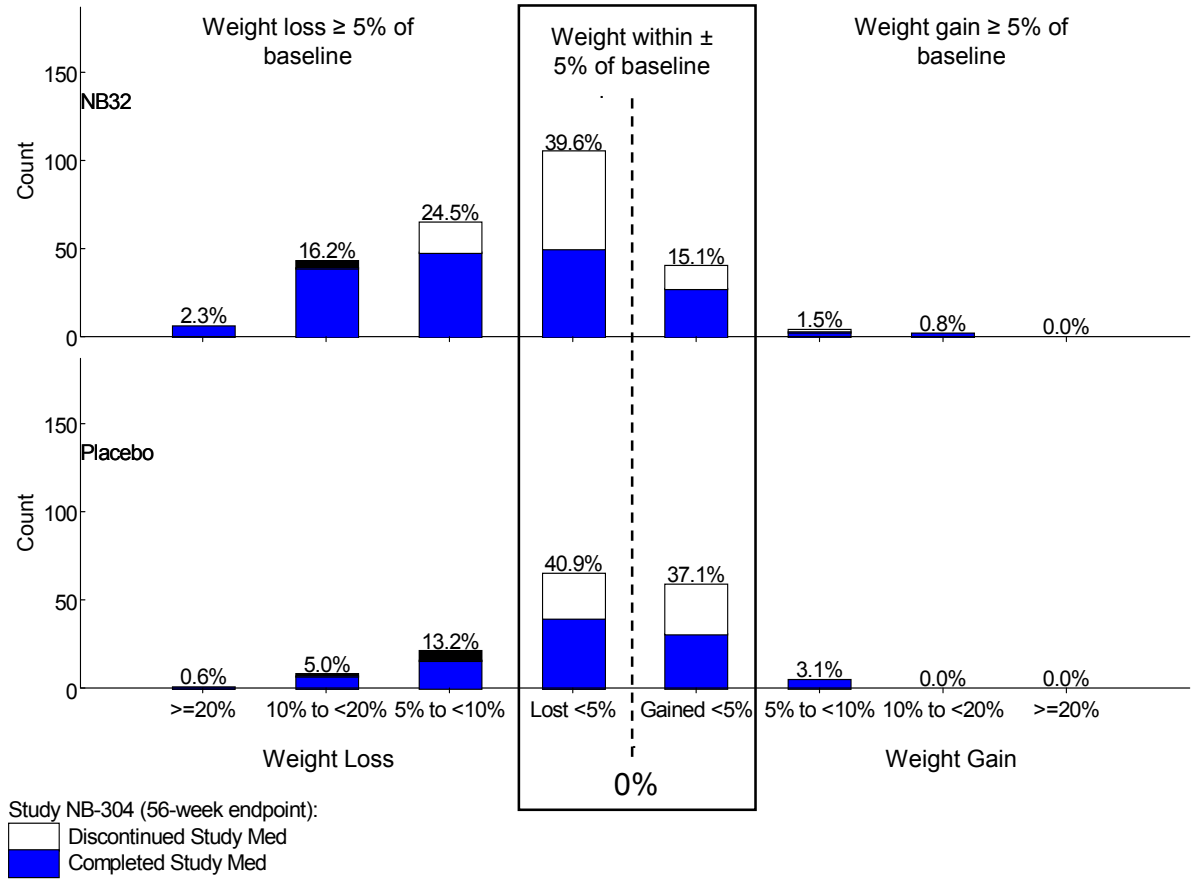


FIGURE 9 Study NB-304; Distribution of weight change at week 56; FAS analysis set



5. CONCLUSIONS ABOUT THE EFFICACY OF CONTRAVE

The results of four Phase 3 studies are consistent and confirm the efficacy of naltrexone 32 mg / bupropion 360 mg compared to placebo after 56 weeks of treatment, in the co-primary weight loss endpoints of average weight loss compared to baseline and the percentage of subjects who lost at least 5% of baseline body weight. Results of alternate analysis models and other versions of the analysis population were consistent with the results from the primary analysis. In my opinion, the applicant used a reasonable set of analyses that explored the effect of different analysis sets and analysis models on the study conclusions.

A significant review issue that affects the estimate of the placebo-adjusted effect of the naltrexone /bupropion combination is the occurrence of a substantial percentage of randomized subjects who discontinued taking study medication prior to week 56. The most frequently cited reason for withdrawing from the naltrexone /bupropion combination was adverse events, and the most frequently cited adverse event was nausea. The median time to withdrawal due to adverse events was 4 weeks in each study, which means that these early withdrawals were not likely to be included in the full analysis database. This limits the extent to which the full analysis database represents the experiences of all randomized subjects. The issue of how to represent early withdrawals is further complicated because some subjects discontinued study medication in the later weeks of a study, after they had lost more than 5% of their baseline body weight. These factors, when taken together, complicate the statistical approach to representing the responses of subjects who discontinued study medication. There may not be one approach to estimating the placebo-adjusted effect of the naltrexone /bupropion combination that fully captures the dynamics of study discontinuation. For this reason, I believe it is useful to evaluate the range of estimates obtained from the sensitivity analysis.

Statistical Review Appendix A: Study NB-201 (Evaluating the Combination Product)

Background: The 2007 weight management guidance references the Code of Federal Regulations (CFR) concerning combination products, which states that two or more products may be combined into a single fixed-dosed combination when each component makes a contribution to the claimed effect or effects (21 CFR 300.50). The guidance recommends further that "the efficacy and safety of fixed dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to compare the maximal or near-maximal weight-management effects of the placebo." The 2007 weight management guidance also states that "Once a fixed-dose combination has been deemed more effective than its individual components, the combination can then be examined versus placebo in phase 3 trials. This approach may preclude the need to include treatment groups for the individual components of the fixed-dose combination product in late-stage preapproval trials." This is the approach that the applicant took, with the concurrence of the Division.

Review: The biometrics team reviewed the statistical analysis plan for Study NB-201 because of its pivotal contribution to the evaluation of the combination product (see review dated 5/31/06). The applicant submitted the results of Study NB-201 prior to initiating the Phase 3 studies, and the Division concurred that the results supported the contribution of each component towards the overall efficacy of the combination (see letter dated 12/7/06).

Design: Study NB-201 was conducted in male and female patients, 18 to 60 years of age, with BMI $\geq$ 30 and $\leq$ 40 kg/m^2. Study drugs were titrated up during the first 4 weeks of blinded treatment to achieve the target dose for each treatment group. However, dose modifications and extended titration periods were permitted in the presence of adverse events and at the investigator's discretion. The primary endpoint was the weight at week 24 expressed as a difference from baseline and as a percentage change from the baseline weight. The study was conducted at 7 sites in the U.S, from 8/1/05 (first patient enrolled) to 12/13/06 (last patient completed). Dose groups, along with the daily dose of each component, are shown below:

- Bupropion 400 mg + Naltrexone 48 mg; n=67
- Bupropion 400 mg + Naltrexone 32 mg; n=70
- Bupropion 400 mg + Naltrexone 16 mg; n=67
- Bupropion 400 mg (monotherapy); n=66
- Naltrexone 48 mg (monotherapy); n=61
- Placebo; n= 88

Study Conduct: Study NB-201 was conducted in two cohorts, with the combination arm with naltrexone 32 mg and additional patients to the placebo arm added in a second cohort after enrollment in the other five arms of the study was underway. The addition of the second cohort allowed for an evaluation of an intermediate dose of naltrexone. The statistical analysis plan was amended prior to unblinding of either cohort, to allow for the analysis of the added combination arm.

Disposition: The percentage of study dropouts ranged from 15.7% to 37.3% in the six arms of the study, with the highest percentage in the Bup+Nal48 combination arm (TABLE 16). The arms that included naltrexone were associated with a higher percentage of dropout than arms without naltrexone. The two arms with the highest percentage of dropouts (Bup+Nal48 and Bup+Nal16) also had the highest percentage of dropouts due to adverse events. The exception to this pattern

is the Bup+Nal32 arm, which had the lowest percentage of dropouts in any arm (15.7). This is the arm that was added to the study as Cohort 2.

TABLE 16 Study NB-201 disposition for the primary treatment period (weeks 1 to 24), randomized population

	Treatment Group Number of subjects, n (%)					
	BPL + NPL N = 88	BPL + Nal 48 N = 61	Bup + NPL N = 66	Bup + Nal 16 N = 67	Bup + Nal 32 N = 70	Bup + Nal 48 N = 67
Study Disposition						
Completed	69 (78.4)	37 (60.7)	45 (68.2)	41 (61.2)	52 (74.3)	36 (53.7)
Terminated early[1]	16 (18.2)	19 (31.1)	15 (22.7)	23 (34.3)	11 (15.7)	25 (37.3)
Not treated	3 (3.4)	5 (8.2)	6 (9.1)	3[2] (4.5)	7 (10.0)	6 (9.0)
Primary reason for early termination						
Enrolled, but did not meet selection criteria	3 (3.4)	5 (8.2)	4 (6.1)	2 (3.0)	7 (10.0)	7 (10.4)
Failure to comply with protocol requirements	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)
Subject moved	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.0)	1 (1.4)	0 (0.0)
Insufficient weight loss	6 (6.8)	1 (1.6)	2 (3.0)	2 (3.0)	0 (0.0)	0 (0.0)
Adverse event	2 (2.3)	4 (6.6)	2 (3.0)	10 (14.9)	3 (4.3)	8 (11.9)
Withdrew consent	2 (2.3)	9 (14.8)	6 (9.1)	5 (7.5)	3 (4.3)	7 (10.4)
Lost to follow-up	6 (6.8)	3 (4.9)	4 (6.1)	5 (7.5)	4 (5.7)	7 (10.4)
Other	0 (0.0)	2 (3.3)	2 (3.0)	0 (0.0)	0 (0.0)	1 (1.5)
Time on study[3]						
0 weeks	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 to 8 weeks	7 (8.0)	11 (18.0)	13 (19.7)	16 (23.9)	13 (18.6)	20 (29.9)
> 8 to 16 weeks	8 (9.1)	8 (13.1)	6 (9.1)	7 (10.4)	3 (4.3)	7 (10.4)
> 16 to 24 weeks	73 (83.0)	41 (67.2)	47 (71.2)	44 (65.7)	54 (77.1)	40 (59.7)

Source: Study NB-201 clinical report, Table 10-1

Analysis populations: The intention-to-treat (ITT) analysis set was defined as all subjects who are randomized and have at least one post-baseline body weight measurement. Missing values at study week 24 were imputed using the last non-missing observation carried forward (LOCF) method.

Primary efficacy endpoint: The primary efficacy endpoint was the percent change from baseline in total body weight, measured between baseline and week 24.

Primary analysis model: The biometrics review team recommended a fully pre-specified analysis plan, because of the pivotal role of Study NB-201 in evaluating the combination therapy (see the letter to the sponsor dated June 14, 2006). Although the biometrics team recommended an analysis of covariance, with baseline body weight as a covariate and treatment group and center as factors in the model, the sponsor pre-specified an analysis of variance with treatment group as the main effect. The statistical analysis plan (SAP) also identified a closed testing sequence for the primary analysis, in the following order: (1) NB48 compared with placebo; (2) NB48 compared with naltrexone monotherapy; and (3) NB48 compared with bupropion monotherapy. Tests were evaluated in sequence, using a two-tailed α of 0.05. The comparisons of NB16 with placebo and monotherapy components were included as exploratory analyses, and the comparisons of NB32 with placebo and monotherapy components were not described in the SAP. This omission was likely due to the inclusion of the NB32 arm in the second cohort of the study.

Efficacy results: Following the pre-specified sequence of testing, we would conclude that the Bup-Nal 48 combination was not supported, because the contribution of the naltrexone 48 component was not statistically significant (TABLE 17, part 1, applicant's pre-specified method). The placebo-adjusted effect of the BN48 combination was an average loss of 3.5% of baseline weight at week 24. This was statistically significant from the placebo arm. The contribution of the bupropion monotherapy component, 3.1%, was statistically significant, but the contribution of the naltrexone 48 mg monotherapy component, 1.7%, was not statistically significant (TABLE 17).

The applicant speculated that "The relatively greater frequency of permanent dose modifications and early treatment discontinuations associated with the higher naltrexone dose used in the NB48 treatment group are likely offsetting potential weight loss effects in this analysis."[7] For this reason they conducted an additional, post-hoc analysis of all three of the Bup-Nal combinations. They evaluated each of the 9 pairwise comparisons involved in this post-hoc analysis at an adjusted α of $0.5/9 = 0.0056$. This post-hoc approach enabled them to evaluate the Bup-Nal 32 and the Bup-Nal 16 combinations. Using this approach, they concluded that the efficacy of both of these combinations was supported, because the monotherapy components were associated with a statistically significant contribution to the average weight loss of the combination (TABLE 17, part 2, post-hoc method).

On the basis of these results, the Division agreed with the applicant that the Phase 3 studies could be conducted with comparisons of NB combinations conducted only with placebo (see letter dated 12/7/06).

[7] Study NB-201 report, part 11.4.1.1

TABLE 17 Study NB-201 primary and post-hoc evaluation of the Bup-Nal combinations at week 24

Combination	vs.	Monotherapy or Placebo	N Comb	N Mono	Baseline mean weight (kg) ± SD Comb	Baseline mean weight (kg) ± SD Mono	Adjusted mean % change from baseline at Week 24 ± SE Comb	Adjusted mean % change from baseline at Week 24 ± SE Mono	Difference in adjusted mean change, Combination – Monotherapy or Placebo LS Mean (95% CI)	P-value
1. Applicant's pre-specified method[1]										
Step 1. BN48	vs.	Placebo	54	84	94.4 ± 13.0	97.9 ± 13.4	-4.3 ± 0.7	-0.8 ± 0.5	-3.5 (-5.2 to -1.9)	<0.0001
Step 2. BN48	vs.	N48		49		96.0 ± 10.6		-1.2 ± 0.7	-3.1 (-5.0 to -1.3)	0.0009
Step 3. BN48	vs.	B		57		98.5 ± 13.1		-2.7 ± 0.6	-1.7 (-3.4 to 0.1)	0.0684
	Decision: The BN48 combination is not supported because the contribution of the naltrexone 48 component is not statistically significant.									
2. Applicant's post-hoc method[2]										
BN48	vs.	Placebo	54	84	94.4 ± 13.0	97.9 ± 13.4	-4.3 ± 0.7	-0.8 ± 0.5	-3.5 (-5.2 to -1.9)	<0.0001
	vs.	N48		49		96.0 ± 10.6		-1.2 ± 0.7	-3.1 (-5.0 to -1.3)	0.0009
	vs.	B		57		98.5 ± 13.1		-2.7 ± 0.6	-1.7 (-3.4 to 0.1)	0.0684
	Decision: The BN48 combination is not supported because the contribution of the naltrexone 48 component is not statistically significant.									
BN32	vs.	Placebo	63	84	95.8 ± 12.6	97.9 ± 13.4	-5.4 ± 0.6	-0.8 ± 0.5	-4.7 (-6.2 to -3.1)	<0.0001
	vs.	N48		49		96.0 ± 10.6		-1.2 ± 0.7	-4.3 (-6.0 to -2.5)	<0.0001
	vs.	B		57		98.5 ± 13.1		-2.7 ± 0.6	-2.8 (-4.5 to -1.1)	0.0015
	Decision: The BN32 combination is supported because the contribution of both components is statistically significant.									
BN16	vs.	Placebo	54	84	95.3 ± 13.8	97.9 ± 13.4	-5.4 ± 0.7	-0.8 ± 0.5	-4.6 (-6.2 to -3.0)	<0.0001
	vs.	N48		49		96.0 ± 10.6		-1.2 ± 0.7	-4.2 (-6.1 to -2.4)	<0.0001
	vs.	B		57		98.5 ± 13.1		-2.7 ± 0.6	-2.7 (-4.5 to -1.0)	0.0026
	Decision: The BN16 combination is supported because the contribution of both components is statistically significant.									

Notes:

[1] Applicant's pre-specified method: Evaluate the three comparisons in the order shown, at a two-tailed α of 0.05. If all three comparisons are statistically significant, conclude that the BN48 combination is supported.

[2] Applicant's post-hoc method: Evaluate all 9 comparisons simultaneously at an adjusted two-tailed α of 0.05/9 = 0.0056.

Source: Study NB-201 clinical report, Table 5.1.1.1c

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 17, 2010
To:	Mary Parks, MD Director, Division of Metabolic and Endocrine Products (DMEP) Office of Drug Evaluation II, Office of New Drugs (OND), CDER
From:	Jo Wyeth, PharmD, Safety Evaluator Division of Pharmacovigilance (DPV) I Office of Surveillance and Epidemiology (OSE), CDER
Through:	Mark Avigan, MD, CM Associate Director, Office of Surveillance and Epidemiology (OSE) Acting Director, Division of Pharmacovigilance (DPV) 1, OSE, CDER Lanh Green, PharmD, MPH, Safety Evaluator Team Leader Division of Pharmacovigilance (DPV) I Office of Surveillance and Epidemiology (OSE), CDER
Subject:	AERS Review
Drug Name(s):	Bupropion/Naltrexone (Contrave)
Application Type/Number:	NDA 200-063
Applicant/sponsor:	Orexigen Therapeutics
OSE RCM #:	2010-926

Table of Contents

1 INTRODUCTION

This review provides an analysis of AERS reports associated with bupropion (Wellbutrin, Zyban, Aplenzin) and naltrexone (Revia, Vivitrol). This analysis focuses on reports describing concurrent use of bupropion and naltrexone, but also provides an overview of the U.S. serious reports associated with bupropion and naltrexone as single agents. The Division of Metabolic and Endocrine Products (DMEP) requested this review to assist in their evaluation of NDA 200-063 (Contrave), a combination product of bupropion and naltrexone for the management of weight loss. An Advisory Committee meeting is scheduled for December 7, 2010 for considering approval of the combination product for weight management.

DMEP's preliminary analysis of the Contrave NDA identified the following relevant safety issues:

1. Cardiac Disorders (myocardial infarction, stroke, coronary revascularization procedure, palpitations, increased blood pressure and or pulse)
2. Ear and Labyrinth Disorders (tinnitus)
3. Gastrointestinal Disorders (nausea, constipation, vomiting, dry mouth, abdominal pain, dysgeusia)
4. Hepatobiliary Disorders (hepatotoxicity and gallbladder disease)
5. Immune System Disorders (hypersensitivity)
6. Musculoskeletal and Connective Tissue Disorders (joint and muscle pain)
7. Nervous System Disorders (seizures, cognitive impairment, dizziness, syncope, headache, tremor, dysgeusia)
8. Psychiatric Disorders (suicidality, depression, anxiety, sleep disorders, agitation)
9. Renal and Urologic Disorders (renal impairment, increase in serum creatinine)
10. Skin and Subcutaneous Tissue Disorders (skin rash, hyperhidrosis)
11. Vascular Disorders (hot flush)

2 BACKGROUND

This section provides the proposed indication and dosage for bupropion/naltrexone (Contrave), and known safety information for bupropion and naltrexone as single agents.

2.1 BUPROPION/NALTREXONE (CONTRAVE)

Orexigen Therapeutics, the sponsor of Contrave (bupropion/naltrexone), is seeking an indication for the treatment of obesity and weight management, including both weight loss and maintenance of weight loss for patients with an initial BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with one or more risk factors (diabetes, dyslipidemia, or hypertension). The proposed Contrave dosage forms are 90 mg/4 mg and 90 mg/8 mg tablets (extended release) for a recommended maintenance dosage of two tablets twice daily (360 mg of bupropion/32 mg of naltrexone total daily dose).

2.2 BUPROPION (WELLBUTRIN, ZYBAN, APLENZIN*) [1,2,3,4]

Bupropion, a relatively weak inhibitor of norepinephrine and dopamine reuptake, was initially approved by FDA in 1985 for the treatment of depression. Since 1985, bupropion has also been approved for use in the management of smoking cessation (Zyban), major depressive disorder (Wellbutrin, Wellbutrin XL, Aplenzin), and seasonal affective disorder (Wellbutrin XL). The usual target dose is 300 mg daily (maximum of 450 mg daily). Bupropion, like other antidepressants, has a boxed warning for suicidality, and a Risk Evaluation and Mitigation Strategy (Medication Guide) for suicidality and seizures.

Safety concerns with bupropion center around the 1) dose-related noradrenergic and dopaminergic effects that are primarily neuropsychiatric (seizures, suicidality, mood changes) and cardiovascular, and 2) idiosyncratic reactions such as allergic reactions and liver injury.

The bupropion labeling advises (WARNINGS AND PRECAUTIONS) of the following:

- Clinical worsening and suicide risk in treating psychiatric disorders (closely monitor patients, particularly children, adolescents and young adults)
- Neuropsychiatric symptoms (serious mood changes, including depression, psychosis, mania, anxiety, and completed suicide) with smoking cessation treatment (events occur in patients with and without psychiatric disease)
- Screen patients for bipolar disorder (treatment with an antidepressant may precipitate a mixed and or manic episode in patients at risk for bipolar disorder)
- Do not use multiple bupropion-containing products
- Seizures:
  - Risk of seizure strongly associated with dose; ~ 0.4 percent of patients treated at doses up to 450 mg/day experienced a seizure; the seizure incidence increases almost tenfold between 450 and 600 mg per day
  - Risk of seizure is related to 1) patient factors [history of prior seizures or head trauma], 2) clinical situations [excessive use of alcohol or sedatives, and patients with diabetes treated with oral hypoglycemics or insulin] and 3) concomitant use of medications known to lower the seizure threshold [antipsychotics, other antidepressants, etc)
  - To reduce risk of seizure, total bupropion daily dose should not exceed 450 mg; each single dose should not exceed 150 mg; increase dose gradually

* Aplenzin contains the hydrobromide form of bupropion. Wellbutrin, Wellbutrin XL, and Zyban contain the hydrochloride form of bupropion.

Bupropion WARNINGS AND PRECAUTIONS continued:

- Hepatotoxicity (animal data suggests an increase in the incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy)
- Neuropsychiatric symptoms, including agitation, insomnia, psychosis, confusion, mania (symptoms sometimes severe and require treatment with sedative/hypnotic drugs or discontinuation of bupropion)
- Weight loss (28 percent of patients treated with bupropion lost > 5 pounds)
- Allergic reactions, including rare postmarket reports of Stevens-Johnson syndrome and anaphylactic shock
- Cardiovascular events (severe hypertension requiring acute treatment reported in patients with or without evidence of pre-existing hypertension; use in caution in patients with history of myocardial infarction or unstable heart disease)
- Hepatic impairment (use with caution in patients with hepatic impairment; extreme caution in patients with severe hepatic cirrhosis)
- Renal impairment (bupropion and associated metabolites may accumulate in patients with renal impairment)
- Drug interactions – bupropion metabolized by CYP2B6, and inhibits CYP2D6; caution using bupropion with drugs known to lower the seizure threshold
- Pregnancy Class C

Bupropion is CONTRAINDICATED in patients:

- With a seizure disorder
- Treated with other medications containing bupropion because the incidence of seizures is dose dependent.
- A current or prior diagnosis of bulimia or anorexia nervosa (higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion)
- Abruptly discontinuing alcohol or sedatives (including benzodiazepines)
- Taking a monoamine oxidase inhibitor

Bupropion Reports in AERS

Serious adverse events associated with bupropion that are frequently reported to AERS (listed in APPENDIX I) are consistent with those described in the bupropion labeling. Of note, between marketing and January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use), the top ten most frequently reported events are Convulsions, Urticaria, Grand Mal Convulsions, Dermatitis, Pruritus, Dyspnea, Tremor, Dizziness, Overdose (intentional and unintentional), and Drug Interaction.

Bupropion Deaths

AERS contains 166 reports of death associated with bupropion that were reported to FDA between the initial marketing approval in 1985 and January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use). The three most frequently reported events associated with a bupropion death are Intentional Overdose or Suicide (80 reports), Cardiac Arrhythmia (18 reports), and Seizure (14 reports). APPENDIX II lists the bupropion reports of death by System Organ Class.

2.3 NALTREXONE (REVIA, VIVITROL)[56]

Naltrexone, initially approved by FDA in 1984, is a reversible opioid antagonist approved for use in the management of alcohol dependence and blockade of the effects of exogenously administered opioids. Naltrexone is available both as an oral tablet (ReVia) and injection (Vivitrol). The recommended oral naltrexone dose is 50 mg once daily, which will block the pharmacologic effects of 25 mg of intravenously administered heroin for up to 24 hours.

Naltrexone has high affinity for mu opioid binding sites, and in the absence of an agonist drug may have limited effects. The naltrexone labeling advises (WARNINGS AND PRECAUTIONS) the following:

- Naltrexone may cause hepatocellular injury, particularly at higher doses (margin of separation between the safe dose of naltrexone and the dose causing liver injury is 5-fold or less; no reports of liver failure have been reported)
- Naltrexone is contraindicated in patients with acute hepatitis or liver failure; use with caution in patients with active liver disease
- Injection site reactions (with Vivitrol, the injectable naltrexone formulation) may be severe (including surgical excision of necrotic tissue)
- Eosinophilic pneumonia (reported in clinical trials with Vivitrol, the injectable naltrexone formulation)
- Patients must be opioid-free for at least 7-10 days before starting naltrexone (consider to administer naloxone challenge test to confirm patient is opioid-free)
- Attempting to overcome naltrexone blockade by administering large amounts of exogenous opioids may lead to a fatal opioid overdose
- Patients with history of opioid use may be more sensitive to lower doses of opioids after naltrexone is discontinued
- If reversal of naltrexone blockade is required, consider regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics, or general anesthesia
- Accidental ingestion of naltrexone by opioid-dependent individuals has resulted in severe opioid withdrawal syndromes
- Caution in patients with renal impairment (naltrexone and its metabolite are excreted primarily in the urine)
- Caution in patients with liver disease (naltrexone AUC increased 5- and 10-fold in patients with compensated and decompensated liver cirrhosis)
- Naltrexone does not abate risk of depression or suicide (risk of suicide increased in patients with substance abuse; depression more common in patients treated with Vivitrol, the injectable naltrexone formulation)
- Pregnancy Class C

Naltrexone is CONTRAINDICATED in patients:

- Receiving opioid analgesics
- Dependent on opioids
- In acute opioid withdrawal
- Who have failed the naloxone challenge test or have a positive urine screen for opioids
- With acute hepatitis or liver failure

Naltrexone Reports in AERS

Serious adverse events associated with naltrexone that are frequently reported to AERS (listed in APPENDIX III) are consistent with the naltrexone labeling. Of note, the top ten most frequently reported events are Vomiting, Nausea, Diarrhea, Death[†], Injection Site Pain, Depression, Drug Ineffective, Drug Withdrawal Syndrome, Condition Aggravated, and Drug Interaction.

Naltrexone Deaths

Since marketing through January 1, 2010, AERS contains 52 naltrexone reports associated with death. The three most frequently reported events associated with a naltrexone death are Suicide, Overdose (unclear if intentional or accidental), and Rapid or Ultra Rapid Detoxification. APPENDIX IV lists the naltrexone reports of death by System Organ Class.

[†] Death is generally reported as an outcome. However, the term, Death is used as a coding term when there is no adverse event reported.

3 METHODS

3.1 AERS SEARCH STRATEGY

AERS was searched on July 5, 2010 using the search criteria in Table 1 below.

Table 1. Search Criteria for Used to Identify Bupropion and Naltrexone (Concomitant Use) Cases in AERS	
Product(s):	Interaction Search Product 1: Bupropion (Wellbutrin, Zyban, Aplenzin) Product 2: Naltrexone (ReVia, Vivitrol) Products-Trade Name: Contrave (separate search)
Search Terms:	All
Search Dates:	Marketing approval for each product through January 1, 2010
Countries:	All (United States & foreign)
Ages:	All
Combination Products:	Yes
Concomitant Products:	Yes
Reason for Use:	All
Outcome:	All (Serious and Nonserious)

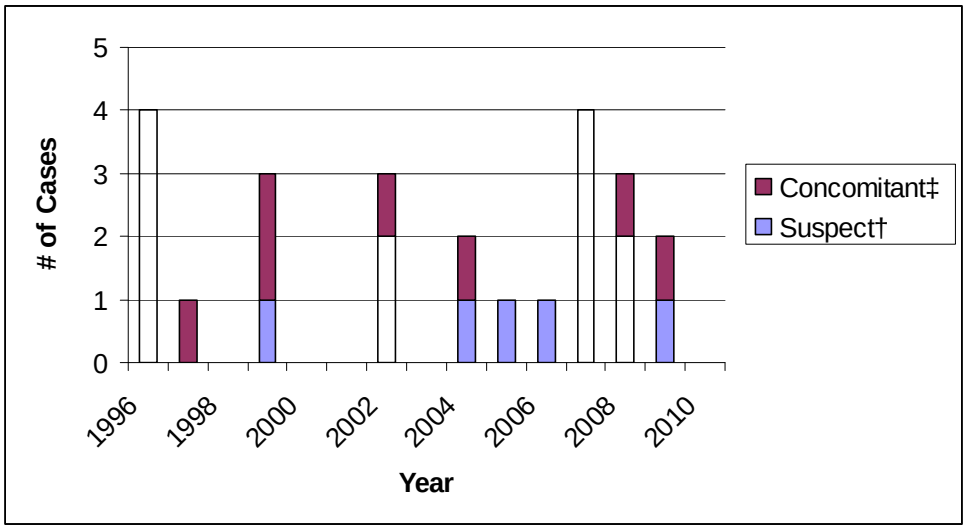
3.2 CASE SELECTION

We limited the AERS reports to spontaneous reports involving a patient on both bupropion and naltrexone. The search strategy in Section 3.1 identified 29 unique cases (US: 26, Foreign: 3), of which we excluded five cases because they were not spontaneous reports (legal reports: 4, solicited: 1). APPENDIX V lists the five excluded cases by ISR number.

4 RESULTS

Using the search criteria and case selection described in Section 3 (Methods), AERS contains 24 cases (US: 21, Foreign: 3) associated with concurrent use of bupropion and naltrexone. Seventeen of the twenty-four cases reported bupropion and or naltrexone as a suspect drug in causing the adverse event, and seven cases reported bupropion and naltrexone as concomitant drugs. No deaths were reported. The 24 cases are presented by FDA receipt year in Figure 1.

Figure 1. AERS Cases (Serious and Nonserious, U.S. and foreign) With Concurrent Use of Bupropion and Naltrexone, by Reported Suspect Drug (n=17) or As Concomitant Drug (n=7) and FDA Receipt Year, Marketing through January 1, 2010



Suspect=bupropion and or naltrexone was identified by the reporter as "suspect" in causing the adverse event

Concomitant=bupropion and naltrexone were listed in the report, but not suspected by the reporter as causing the adverse event

Table 4 presents the characteristics of the 24 cases involving concurrent use of bupropion and naltrexone. None of the cases suggested bupropion and or naltrexone were prescribed for weight management. None of the cases implicated both bupropion and naltrexone as suspect in having caused the adverse event. However, attribution was difficult because of the concomitant use of multiple medications, and presence of underlying drug and or alcohol abuse. APPENDIX IV provides a brief description of the 24 cases.

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Bupropion and Naltrexone (n=24). Source: AERS, Marketing Through January 1, 2010

Characteristic		
Reporting Country	United States	21
	Foreign	3
Age (yrs)	<30 yrs	6
Median: 44	30-39 yrs	3
Range: 14- 60	40-49 yrs	11
n=24	50-59 yrs	3
	60+ years	1
	Age not reported	--
Gender		
Percent Female: 50	Female	12
	Male	12
Weight (kg)		
Median: 74	40-59	1
Range: 42 - 102	60-79	5
n=10	80-100	3
	>100 kg	1
	Weight not reported	14
Reported Reason for Use		
	Mental Health Disorder	6
	Drug and or Alcohol Abuse	5
	Smoking Cessation	4
	Reason for Use Not Reported	9

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Bupropion and Naltrexone (n=24). Source: AERS, Marketing Through January 1, 2010
Reported Suspect Drug*: Bupropion (6), Naltrexone (11), Other (7)
Reported Events For the 6 Cases Listing BUPROPION as the Suspect Drug* (brand name, dose, and time to event or duration of therapy) Acute Hepatitis (bupropion 300 mg daily x 1 month) Anxiety, Suicidal Ideation, Mood Change (Zyban 150 mg x 4 months) Rash, Sore Throat and Tongue (Wellbutrin XL 150 mg daily x 2 weeks) Amenorrhea (Wellbutrin SR 100 mg BID x unknown duration) Swollen Hands, Itching, Aggravation, Hyperactivity, Blurred Vision (Wellbutrin 150 mg BID x 1 wk) Headache, Nausea, Dry Mouth, Leg Twitching (Zyban 150 mg daily or BID x 3 months)
Reported Events For the 11 Cases Listing NALTREXONE as the Suspect Drug* (brand name, dose and duration of therapy or time to event) Abnormal Feeling, "Dilated Pupils," Abdominal Pain, Insomnia (Revia 50 mg daily x 1 dose) Weight Loss and Anorexia (Revia 25 mg BID x 4 months) Bone Pain, Abdominal Pain, Nausea, Insomnia (Revia 50 mg daily x 2 days) Agitation, "Feeling Uptight and Excited" (Revia 50 mg daily x 2 months) Tendonitis, Medial Epicondylitis, Back Pain (Revia 50 mg daily x 1 month) Pancreatic Cyst (Revia 75 mg daily x 9 months) Cancer, Laryngeal (Vivitrol unk dose x 6 months) Pneumonia and Sepsis (Vivitrol 380 mg IM monthly, 2 days after 3rd injection) Blurred Vision, "Seizure," Vomiting, "Coma," "Pneumonia" (Vivitrol 380 mg IM x 1 dose) Dizziness, Respiratory Nausea, Depression, Delirium, Aggression (Vivitrol 380 mg IM x 1 dose) Injection Site Reaction (Vivitrol 380 mg IM monthly x 2 months)
Reported Events For the 7 Cases Listing Bupropion/Naltrexone As Concomitant Drugs (suspect drug listed in parentheses) Premature Ejaculation (methylphenidate) Akathisia (thioridazine) Urine Drug Screen Positive (venlafaxine) Hyponatremia (oxcarbazepine) In Utero Exposure (lithium) Worsening Depression (varenicline) "Swollen" Tongue, Mouth and Lips; Memory Impairment; Mood Change (lisdexamfetamine)

* Suspect Drug=the drug was suspected by reporter to have caused the adverse event

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Bupropion and Naltrexone (n=24). Source: AERS, Marketing Through January 1, 2010
Reported Medical History† -Alcohol/Drug Abuse or Addiction (10) -Mood Disorder (depression, bipolar, panic disorder, self injurious behaviors) (10) -Attention Deficit Hyperactivity Disorder (2) -Cardiac Disorder (HTN, arrhythmia, or taking cardiac drugs) (4) -Respiratory Disorder (asthma, COPD, smoking) (5) -Medical history not reported (5)
Reported Medication History† Antiepileptics (VPA, gabapentin, zonisamide, topiramate, lamotrigine): 9 Antidepressants (SSRI, SNRI, TCA): 5 Benzodiazepines: 4 Antipsychotics: 4 Lithium: 1 Cardiac medications (beta blocker, ARB, terazosin): 4 Trazodone: 3 Other: PPI (4), buspirone (3), H2Blocker (1), Chantix (1), opioid (1)

†Numbers may not sum because cases may report more than one comorbidity or concurrent medication

5 DISCUSSION

Given two-third of adults in the United States are either overweight or obese,[7] weight loss products, such as Contrave, may have widespread exposure, and the potential for associated safety issues must be considered.

Although the Contrave labeling defines the intended population (overweight or obese), other characteristics of the population using Contrave is not known. Thus, there exists a potential for exposure to women of childbearing age, and significant drug interactions (bupropion is metabolized by CYP2B6 and inhibits CYP2D6). This review also identified other important safety concerns (described in the bupropion and or naltrexone labelings) that include seizures, suicidality, cardiovascular events, and liver injury. Further, the safety profile associated with long term use of Contrave is not known.

As part of the Contrave NDA, the sponsor submitted a postmarket safety analysis of bupropion and naltrexone.[8] The sponsor concluded, "key safety signals including the risk of suicidality with antidepressants, seizures with bupropion, and use of naltrexone with opiates are well-described in the prescribing information." However, the sponsor's analysis and conclusions were based on AERS line listings and data mining algorithms, which are insufficient for FDA to have a comprehensive understanding of each product's safety profile.

6 CONCLUSIONS AND RECOMMENDATIONS

Both bupropion and naltrexone have been approved as single ingredient products in the United States for more than 20 years. However, little is known about the postmarket safety profile when bupropion and naltrexone are used for weight management. Contrave could have widespread use, and the potential for safety issues (including seizures, suicidality, and cardiovascular events) cannot be dismissed.

Approval of Contrave, based on benefit and risk, should take into account the safety profile not only of the combination product, but the individual components as well. The sponsor submitted a Summary of Clinical Safety that included a postmarket analysis of bupropion and naltrexone. However, the analysis is insufficient for FDA to have a comprehensive understanding of Contrave's safety profile when used in the targeted overweight or obese population.

The Division of Pharmacovigilance (DPV) recommends DMEP consider requesting the sponsor submit to FDA for review, an integrated safety summary (ISS) that contains separate sections for bupropion and naltrexone, and is organized by targeted safety topics. For bupropion, the serious targeted safety topics include seizures, cardiac arrhythmias, hypertension, stroke, suicidality and other psychiatric disorders, cognitive impairment, use in special patient populations (including exposure during pregnancy), misuse (including

overdose), allergic reactions, drug interactions (including use with other bupropion-containing products, drugs that lower the seizure threshold, and drugs metabolized by CYP2D6), and long term exposure. For naltrexone, the targeted safety topics include, but are not limited to, use in special patient populations (including exposure during pregnancy), drug interactions (including opioids), overdose, hypersensitivity, and long term exposure.

For each of these drug-specific safety topics, the sponsor would consider postmarket reports, clinical trial data, and worldwide literature to provide the following information (separately) for naltrexone and bupropion in an ISS:

1. Introduction
   - Description of safety topic
   - Labeling relative to the safety topic
2. Background
   - Epidemiology
   - Possible causative agents
   - Other relevant clinical and nonclinical information
3. Experience (with the drug and safety topic of interest)
   - AERS or other postmarket reports
   - Fatalities (tabular summary and narrative descriptions)
   - Serious nonfatal cases
4. Review of Literature
5. Summary and Conclusions
6. References

The sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS), which could include a Medication Guide that is in line with the bupropion labeling. DPV defers to the Divisions of Epidemiology (DEPI) and Risk Management (DRISK) to assist in the review of such proposed REMS and any postmarket studies.

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[1] GlaxoSmithKline. Wellbutrin (bupropion hydrochloride) prescribing information. Greenville, NC. 2009.

[2] GlaxoSmithKline. Zyban (bupropion hydrochloride, sustained-release tablets) prescribing information. Greenville, NC. 2009.

[3] GlaxoSmithKline. Wellbutrin XL (bupropion hydrochloride, extended-release tablets) prescribing information. Greenville, NC. 2009.

[4] Sanofi Aventis. Aplenzin (bupropion hydrobromide, extended-release tablets) prescribing information. Bridgewater, NJ. 2009.

[5] Alkermes, Inc. Vivitrol (naltrexone for extended release injectable suspension) prescribing information. Cambridge, MA. 2009.

[6] Dupont Pharma. Revia (naltrexone hydrochloride tablets) prescribing information. 1999.

[7] Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA.* 2010;303(3):235-241.

[8] King A, Olesen A, Garrard E for the Drug Safety Alliance Inc. A post-marketing adverse drug event profile: bupropion and naltrexone (prepared for Orexigen Therapeutics, Inc.). 2010 Mar 9; 82 p.

APPENDIX I. Bupropion: Frequently Reported Adverse Events

Top 25 Serious Adverse Events (Crude Counts) Reported with BUPROPION, Organized by System Organ Class (SOC) and Preferred Term. Source: AERS, U.S. Cases, Marketing Approval in 1985 Through January 1, 2002*

SOC	Preferred Terms (crude counts)	Total Counts for SOC
Gastrointestinal Disorders		
	Nausea (91), Vomiting (81)	172
General Disorders and Administration Site Disorders		
	Drug Interaction (102), Chest Pain (94), Pyrexia (93), Facial Edema (75)	364
Immune System Disorders		
	Hypersensitivity (108)	108
Injury, Poisoning, and Procedural Complications		
	Intentional Overdose (120), Overdose (107)	227
Musculoskeletal and Connective Tissue Disorders		
	Arthralgia (86)	86
Nervous System Disorders		
	Convulsion (550), Grand Mal Convulsion (179), Tremor (130), Dizziness (123), Headache (103), Amnesia (73)	1158
Psychiatric Disorders		
	Insomnia (94), Confusional State (92), Depression (82), Anxiety (80), Agitation (75)	423
Respiratory, Thoracic and Mediastinal Disorders		
	Dyspnea (158)	158
Skin and Subcutaneous Disorders		
	Urticaria (274), Dermatitis (179), Pruritus (177)	630

*AERS was searched on July 6, 2010 for bupropion reports (U.S. serious only) using the generic (bupropion) and brand names (Wellbutrin, Zyban, Aplenzin). The cut off date was January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use).

APPENDIX II. Listing of U.S. Bupropion Deaths by System Organ Class (n=166)*

Reported Event Associated with Death By System Organ Class (SOC) (number of AERS reports)
Cardiac Disorder (19)
Myocardial Infarction (6), Cardiac Arrest (5), Arrhythmia (4), Sudden Death (2), Left Ventricular Hypertrophy (1), Cardiomyopathy (1)
Hepatobiliary Disorders (2)
Acute Liver Failure (1), Acute Hepatotoxicity (1)
Injury Poisoning and Procedural Complications (21)
Overdose, Unknown if Accidental or Unintentional (16), Accidental Overdose (1), Post-Surgical Procedure (2), MVA (1), Medication Error (1)
Nervous System Disorders (18)
Seizures (14)
Cerebrovascular Accident (1), Neuroleptic Malignant Syndrome (1), Parkinsons disease (1), Cerebral Angitis (1)
Psychiatric Disorders (63)
Intentional Overdose or Suicide (63)
Skin and Subcutaneous Tissue Disorders (1)
Toxic Epidermal Necrosis (1)
Other SOC (14)
In Utero Exposure (7) Respiratory, Thoracic and Mediastinal Disorders (3), Neoplasm, Cervical (1), Sepsis with ESRD(1), Airway Obstruction (1), Hyponatremia (1)
Unknown (28)

*AERS was searched on July 6, 2010 for bupropion reports (U.S. serious only) using the generic and brand names. The cut off date was January 1, 2002 (cutoff date chosen because of stimulated reporting associated with communications regarding an increased risk of suicidality with antidepressant use).

APPENDIX III. Naltrexone: Frequently Reported Adverse Events

Top 25 Serious Adverse Events Reported with NALTREXONE, Organized by System Organ Class (SOC) and Preferred Term. Source: AERS, U.S. Cases, Marketing approval in 1984 through January 1, 2010.*

SOC	Preferred Terms (crude counts)	Crude Counts
Gastrointestinal Disorders		78
	Vomiting (29), Nausea (28), Diarrhea (21)	
General Disorders and Administration Site Disorders		145
	Death (21), Injection Site Pain (20), Drug Ineffective (19), Drug Withdrawal Syndrome (18), Condition Aggravated (17), Drug Interaction (17), Asthenia (11), Injection Site Reaction (11), Pain (11)	
Musculoskeletal and Connective Tissue Disorders		11
	Myalgia (11)	
Nervous System Disorders		28
	Convulsion (16), Dizziness (12)	
Psychiatric Disorders		117
	Depression (19), Agitation (14), Anxiety (14), Drug Dependence (14), Completed Suicide (13), Hallucination (11), Suicidal Ideation (11), Suicide Attempt (11), Alcohol Withdrawal Syndrome (10)	

*AERS was searched on July 6, 2010 for naltrexone reports (U.S. serious only) using the generic (naltrexone) and brand names (ReVia, Vivitrol). The cut off date was January 1, 2010.

APPENDIX IV. Listing of U.S. Naltrexone Deaths by System Organ Class (SOC) (n=52)*

Reported Event Associated with Death By System Organ Class (number of AERS reports)
Cardiac Disorders (3)
Arrhythmia (3)
Hepatobiliary Disorders (2)
Liver Injury (2)
Injury, Poisoning, and Procedural Complications (18)
Rapid or Ultra Rapid Detoxification with Naltrexone (8, of which 7 were associated with subcutaneous naltrexone implant)
Overdose, unclear if intentional or accidental (8)
Hyperthermia or Head Trauma Secondary to Alcohol Abuse (2)
Psychiatric Disorders (7)
Suicide (7)
Respiratory, Thoracic, and Mediastinal Disorders (2)
Respiratory Arrest (2)
Other (7)
Cancer (4), GI Bleed (2), Pancreatitis (1)
Unknown (12)

*AERS was searched on July 6, 2010 for naltrexone reports (U.S. serious only) using the generic (naltrexone) and brand names (ReVia, Vivitrol). The cut off date was January 1, 2010.

APPENDIX V. Excluded Cases (n=5)

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	Reason for Exclusion
4273110 US 2003	30 Female	Paroxetine (Paxil)	Withdrawal symptoms	Attorney report
6194597 US 2009	24 Male	Quetiapine (Seroquel), olanzapine (Zyprexa)	Suicidality, MI, LVH	Attorney report
6271935 US 2007	34 Female	Quetiapine (Seroquel), olanzapine (Zyprexa)	Pancreatitis	Attorney report
6371601 US 2008	38 Female	Quetiapine (Seroquel)	Pancreatitis	Attorney report
6322643 US 2009	62 Male	Niacin (Niaspan)	Flushing	Solicited report

APPENDIX VI. Concurrent Use Cases (n=24)

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
1684232 US 1996	20 Female	**Naltrexone** (ReVia) 50 mg QD	"Feeling Weird," "Dilated" Pupils," Stomachache, Insomnia	Opioid addiction/ bupropion (Wellbutrin)	Unknown
1684469 US 1996	14 Female	**Naltrexone** (ReVia) 25 mg BID (inc from 12.5 mg QD)	Weight Loss, Anorexia	Self injurious behavior, ADHD, seizure disorder/ valproic acid, bupropion (Wellbutrin)	Methylphenidate DC; not yet recovered
1845629 US 1996	37 Male	**Naltrexone** (ReVia) 50 mg QD	Bone Pain, Stomach Cramps, Nausea, Insomnia	Opioid addiction/ bupropion (Wellbutrin), amitriptyline	Unknown
1854107 US 1996	48 Male	**Naltrexone** (ReVia) 50 mg QD	Agitation, "Feeling of Uptight and Excited"	Alcoholism, Depression/ bupropion (Wellbutrin)	Naltrexone DC and "patient returned to normal"
3332428 US 1999	44 Male	**Bupropion** (Zyban) 150 mg QD or BID	HA, Nausea, Dry Mouth, Leg Twitching	Smoking/ trazodone, clonazepam, ranitidine, naltrexone	Bupropion continued, events unresolved
4019004 US 2002	22 Male	**Naltrexone** (ReVia) 50 mg QD	Tendonitis, Back Pain, Medical Epicondylitis	Drug abuse/ valproic acid, bupropion (Wellbutrin SR), risperidone	Symptoms improved by "about 30 %;" Unclear if naltrexone continued
4019006 US 2002	45 Female	**Naltrexone** (ReVia) 75 mg QD	Pancreatic Cyst	Alcoholism, depression, GI ulcer NOS, pancreatitis/ bupropion (Wellbutrin SR)	Continuing naltrexone, but "will be tapered off"

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
4270112 US 2004	42 Male	**Bupropion** (Wellbutrin) 150 mg BID	Swollen Hands, Itching, Irritation, Aggravation, Blurred Vision, Hyperactivity	Depression, smoking/ naltrexone NOS	Bupropion DC; events continued
4839744 US 2005	24 Female	**Bupropion** (Wellbutrin SR) 100 mg BID	Amenorrhea	Depression, cocaine abuse, bipolar/ naltrexone, risperidone, buspirone, topiramate	Bupropion continued, amenorrhea unresolved
5168225 CA 2006	60 Female	**Bupropion** (Wellbutrin XL) 150 mg QD	Rash, Sore Throat, Sore Tongue	---/ fluoxetine 20 mg TIW, losartan 50 mg BID, imiquimod, naltrexone 50 mg QD, celecoxib 200 mg QD, lansoprazole 30 mg QD, oxazepam 15 mg QD, steroid inhaler	Bupropion DC; treated in ER with diphenhydramine; events improved
5261930 US 2007	52 Male	**Naltrexone** (Vivitrol)	Laryngeal Cancer	Alcoholism, COPD, HTN, laryngeal CA/ bupropion (Wellbutrin), rosuvastatin, ramipril, Advair, baclofen, ondansetron, chemotherapy NOS	"Died of sepsis secondary to becoming immunocompromised following chemotherapy"
5298490 US 2007	43 Male	**Naltrexone** (Vivitrol) 380 mg IM QM	Pneumonia, Sepsis	--- bupropion (Wellbutrin XL), Chantix	Naltrexone and bupropion DC; hospitalized and recovered
5343687 US 2007	48 Male	**Naltrexone** (Vivitrol) 380 mg IM QM	Blurred Vision, Self-Reported Seizure, Vomiting, "Coma," pneumonia	Panic attacks, depression, alcohol dependence/ diazepam, bupropion (Wellbutrin), hydrocodone, methadone, sertraline	Hospitalized, and Improving

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
5486406 US 2007	49 Female	**Naltrexone** (Vivitrol) 380 mg IM QM	Lightheadedness, Dizziness, Nausea, Delirium, Respiratory Depression, Aggression	Hypothyroidism, hyperlipidemia, bipolar, migraines,alcoholism/ lamotrigine, lithium, quetiapine, bupropion (Wellbutrin SR), venlafaxine, levothyroxine, atorvastatin, Lyrica, sumatriptan	Hospitalized, and discharged
5660496 US 2008	48 Female	**Naltrexone** (Vivitrol) 380 mg IM QM	Injection Site Reaction	Alcohol dependence/ bupropion (Wellbutrin XL), quetiapine, buspirone, acamprosate,	Naloxone DC; treated with steroids and NSAIDS
5948512 ES 2008	48 Male	**Bupropion** 300 mg QD	Published case report of acute hepatitis (hepatomegaly of 2 cm and mucocutaneous jaundice)	---/ disulfiram, naltrexone	Bupropion DC; event resolved
6192016 FI 2009	53 Male	**Bupropion** (Zyban) 150 mg unknown frequency; Isoniazide unknown dose	Anxiety, Suicidal Ideation, Mood Change	Smoking, latent TB, rheumatic disease/ naltrexone, etanercept	Hospitalized; treated with mirtazapine; events continue
1932464 US 1997	23 Male	Methylphenidate SR 20 mg	Premature Ejaculation	Drug and alcohol abuse, ADHD/ bupropion (Wellbutrin), valproic acid, naltrexone (ReVia)	Unknown
3240459 US 1999	47 Female	Thioridazine 50 mg QD	Akathisia	Bipolar disorder/ naltrexone 50 mg QD, bupropion (Wellbutrin) 150 mg QD, gabapentin 400 TID, clonazepam 1 mg BID	Thioridazine DC and akathisia subsided in 48 hours

ISR # Source RCV Yr	Age (yr) Gender	Reported Suspect Drug	Reported Event	PMH/ Concurrent Drugs	Outcome
3332082 US 1999	21 Female	Venlafaxine 75 mg BID	Urine drug screen positive for PCP	Alcohol and drug addiction/ bupropion (Wellbutrin) 150 mg QD, naltrexone 50 mg QD, gabapentin 800 mg QD, trazodone 100 mg QHS	Unknown
3919300 US 2002	48 Female	Oxcarbazepine 300 mg BID and 600 mg QHS	Hyponatremia	EBV, arrhythmia, s/p TIA, asthma/ quetiapine 700 mg QD, naltrexone 25 mg BID, bupropion SR 100-200 mg QD, panteprazole 40 mg QD, atenolol 25 g QHS, inhalers	Oxcarbazepine DC; salt intake increased
4340824 US 2004	30 Female	Lithium (Eskalith) 450 mg BID	Drug Exposure During Pregnancy (7 weeks gestation)	Manic-depressive/ naltrexone, bupropion (Wellbutrin SR), zonisamide	Reporter referred to the Wellbutrin Pregnancy Registry
5756217 US 2008	55 Male	Varenicline (Chantix) 1 mg BID	Worsening Depression	---/ naltrexone, bupropion (Wellbutrin), buspirone, valproic acid 500 mg BID, lansoparazole 30 mg QD, indomethacin 50 mg BID, cyclobenzaprine 10 mg QD, terazosin 2 mg BID, inhalers	Varenicline DC; outcome unknown
6441117 US 2009	39 Female	Lisdexamfetamine (Vyvanse) 60 mg QD	"Swollen" Tongue, Mouth, and Lips; Memory Impairment, Mood Change	"---/ escitalopram 20 mg, bupropion (Wellbutrin) 300 mg, naltrexone 50 mg, trazodone 100 mg	Lisdexamfetamine DC; symptoms subsided

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

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

/s/

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Guidance for Industry

Developing Products for Weight Management

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Eric Colman at 301-796-1190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2007
Clinical/Medical

Revision 1

Guidance for Industry

Developing Products for Weight Management

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Guidance for Industry[1]
Developing Products for Weight Management

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to industry regarding the development of drugs and therapeutic biologics (hereafter *products*) regulated within the Center for Drug Evaluation and Research (CDER) in the Food and Drug Administration (FDA) for the indication of weight management. This guidance applies to products intended to be used for medical weight loss, which can be defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipids, and HbA1c. This guidance revises the draft *Guidance for the Clinical Evaluation of Weight-Control Drugs* that issued in September 1996. When finalized, this guidance will replace the September 1996 draft guidance.

The September 1996 draft guidance is being revised to provide advice on conducting studies to evaluate the efficacy and safety of products for weight management in patients with medication-induced weight gain and weight management in obese pediatric patients. Recommendations on the design of studies evaluating the efficacy and safety of combinations of weight-management products are also provided.

This guidance does not explicitly discuss indications for weight loss or maintenance of lost weight (which also can be described as prevention of weight regain); however, weight loss and weight maintenance should be demonstrated over the course of at least 1 year before a product can be considered effective for weight management. Thus, the weight management indication incorporates and signifies weight loss and weight maintenance.

[1] This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

This guidance also does not discuss the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In January 2004, the FDA issued a notice in the *Federal Register* requesting public comment on the September 1996 draft guidance for the purpose of incorporating the latest scientific and clinical advances in weight management drug development. In September 2004, the FDA convened an advisory committee meeting to discuss the public comments received and to identify specific scientific, clinical, and regulatory issues that should be included in an updated guidance.

As a result, this revised guidance discusses several key areas of interest that are not covered in the September 1996 draft guidance. These areas include recommendations on the development of products for weight management in pediatric patients and in patients with medication-induced weight gain, and recommendations on the development of combinations of weight-management products.

III. OVERWEIGHT AND OBESITY CLINICAL BACKGROUND

A. The Adult Population

Obesity is a chronic, relapsing health risk defined by excess body fat. The pathogenesis of obesity involves the interaction of genetic, environmental, and behavioral factors. Total body fat can be accurately measured using hydrodensitometry and dual-energy x-ray absorptiometry (DEXA). Because body mass index (BMI), expressed as kilograms of weight divided by height in meters squared (kg/m^2), is simple and inexpensive to calculate, and correlates strongly with total body fat in non-elderly adults, it is commonly used as a surrogate for total body fat.

Excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers (Caterson and Hubbard et al. 2004; Calle and Thun et al. 1999). The relationships between BMI and risks for death and major comorbidities vary by age, sex, race, and smoking status, but, in general, are lowest in individuals with BMIs of 18.5 kg/m^2 to 24.9 kg/m^2 and increase in a curvilinear or linear manner with BMIs of 25 kg/m^2 to approximately 40 kg/m^2.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www fda.gov/cder/guidance/index.htm.

Based on data relating BMI to mortality risk, the World Health Organization in 1995 and the National Institutes of Health in 1998 adopted the weight classifications by BMI that are shown in Table 1 (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998).

Table 1. Weight Classification Guidelines

Classification	**BMI**
Underweight	< 18.5 kg/m^2
Normal weight	18.5 kg/m^2 – 24.9 kg/m^2
Overweight	25 kg/m^2 – 29.9 kg/m^2
Obesity (class 1)	30 kg/m^2 – 34.9 kg/m^2
Obesity (class 2)	35 kg/m^2 – 39.9 kg/m^2
Extreme obesity (class 3)	$\geq$ 40 kg/m^2

An increased level of visceral or intra-abdominal adiposity, independent of BMI, increases the risk for metabolic derangements and perhaps cardiovascular disease (Janssen and Katzmarzyk et al. 2004; Rexrode and Carey et al. 1998; Zhu and Wang et al. 2002). Visceral fat content can be accurately measured with computed tomography (CT) or magnetic resonance imaging (MRI). Waist circumference, like BMI, is inexpensive and easy to measure and correlates with CT- and MRI-derived measurements of visceral fat content (Pi-Sunyer 2004). In general, a waist circumference greater than 40 inches (greater than 102 cm) in men and greater than 35 inches (greater than 88 cm) in women is accepted as indicating increased visceral adiposity (The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 2000).

In overweight and obese individuals, particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss greater than or equal to 5 percent following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis and Macie et al. 2005).

Although some, but not all, observational studies suggest that modest degrees of intentional weight loss in overweight and obese individuals can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality, at the time of this writing, there are no data from randomized, controlled trials on the effects of drug-induced weight loss on these clinical outcomes (Parker and Folsom 2003; Eilat-Adar and Eldar et al. 2004; Gregg and Gerzoff et al. 2003).

Lifestyle modification, consisting of changes in patterns of dietary intake, exercise, and other behaviors, is considered the cornerstone of overweight and obesity management. Because all drug and biological therapies impose some risk for adverse events, the use of a weight-management product should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the anticipated benefits of weight loss are expected to outweigh the known and unknown risks of treatment with a particular weight-management product.

Patients with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by weight-related comorbidities historically have been considered appropriate populations for treatment with weight-management medications (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998). Although these patient-selection criteria are to a degree arbitrary, and an argument may be made for criteria that are more or less restrictive, we believe that individuals with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by weight-related comorbidities represent patient groups with sufficient baseline risk to justify inclusion in studies of investigational weight-management products.

B. The Pediatric Population

As in adults, BMI correlates with more direct measures of adiposity in children and adolescents (American Academy of Pediatrics 2003; Barlow and Dietz 1998; Dietz and Robinson 2005; Speiser and Rudolf et al. 2005). Also similar to adults, BMI correlates with obesity-related comorbidities such as hypertension, dyslipidemia, and type 2 diabetes mellitus in pediatric patients.

In contrast to adults, the terms overweight and obese are used synonymously in pediatric patients (American Academy of Pediatrics 2003). The American Academy of Pediatrics (AAP) defines a pediatric-aged patient with an age- and sex-matched BMI of greater than or equal to 95th percentile as overweight or obese.

For patients aged 2 to 7 years, the AAP recommends weight loss through lifestyle modification if the BMI is greater than or equal to the 95th percentile for age and sex with the presence of one or more comorbidities. For patients who are 7 years of age or older, weight loss through lifestyle modification is recommended if the BMI is between the 85th and 95th percentile for age and sex with the presence of one or more comorbidities or if the BMI is greater than or equal to the 95th percentile for age and sex regardless of the presence of comorbidities.

Before therapeutic intervention, pediatric patients should receive a medical assessment to identify genetic (e.g., Prader-Willi syndrome) or endocrinologic (e.g., Cushing's syndrome) causes of their obesity. Patients also should be screened for the presence of comorbidities such as hypertension, glucose intolerance, and dyslipidemia.

The use of weight-management products in pediatric patients, as in adults, should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the expected benefits of weight loss are believed to outweigh the known and unknown risks of treatment with a particular weight-management product. Such a population might include obese pediatric patients with weight-related comorbidites.

IV. CLINICAL ASSESSMENT OF WEIGHT-MANAGEMENT PRODUCTS IN ADULT PATIENTS

A. Phase 1 and Phase 2 Trials

Before initiating phase 3 clinical trials, the pharmacokinetics and dose-response profiles of a new weight-management product should be well-characterized. Because excess adiposity may influence a product's metabolism and disposition, the pharmacokinetics profile of a weight-management product should be examined in patients with a broad range of BMIs (e.g., 27 kg/m^2 to 35 kg/m^2) (Cheymol 2000). To increase the likelihood of identifying the most appropriate dose for the pivotal clinical trials, early phase clinical studies should include a range of doses and be designed to identify no-effect and maximally tolerated doses. Studies should be designed to differentiate the efficacy of all the active doses versus placebo. The duration of the phase 2 trials should be sufficient to capture the maximal or near-maximal weight loss effects of the active doses. Forethought should be given to whether the product will be ultimately used in a fixed-dose or dose-titration scheme, as this dosing decision will also influence the size and duration of the studies.

Patients included in the early phase efficacy and safety studies generally should have BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by comorbidities. The primary efficacy endpoints should be a comparison of the mean absolute or percent change in body weight between the active-product and placebo-treated groups and the proportion of patients in each treatment group who lose greater than or equal to 5 percent of baseline weight. The effects by dose of the weight-management product on common weight-related comorbidities also should be examined and taken into account when choosing the most appropriate dose for the phase 3 studies.

B. Phase 3 Clinical Trials

1. Trial Design and Patient Populations

In general, phase 3 clinical trials examining the efficacy and safety of weight-management products should be randomized, double-blind, and placebo-controlled. The lifestyle modification programs used in the preapproval trials should be applicable to individual patients prescribed the product post-approval (i.e., programs should strike an appropriate balance between effectiveness and simplicity).

In general, patients should have or be at significant risk for weight-related morbidity and mortality. Such patients include those with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 in the presence of comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea, cardiovascular disease).

Effort should be made to include in the studies a representative sample of patients from the various demographic, ethnic, and racial groups in which the prevalence of obesity is highest. Development programs also should include a representative sample of patients with extreme obesity (BMI greater than 40 kg/m^2).

2. Trial Size and Duration

The number of subjects necessary to demonstrate the efficacy of a weight-management product will be smaller than the number needed to adequately assess safety. A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment.

For example, the above sample size will provide 80 percent power to rule out with 95 percent confidence an approximately 50 percent increase in the incidence of an adverse event that occurs at a rate of 3 percent in the placebo group (i.e., 4.5 percent versus 3 percent). This sample size also should allow for efficacy and safety analyses to be conducted within important subgroups such as sex, ethnicity, and baseline BMI.

3. Efficacy Endpoints

a. Primary efficacy endpoint

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- Mean: The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group.

- Categorical: The proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group.

b. Secondary efficacy endpoints

Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic parameters:

- Blood pressure and pulse
- Lipoprotein lipids
- Fasting glucose and insulin
- HbA1c (in type 2 diabetics)
- Waist circumference

In clinical practice, waist circumference is used as an indirect measure of visceral fat content, which when increased is associated with an elevated risk for metabolic abnormalities such as dyslipidemia and diabetes. Because the evaluation of investigational weight-management products routinely includes assessment of changes in patients' metabolic profiles, and in some cases may involve measurement of visceral fat content by CT or MRI, waist circumference should not serve as a surrogate for visceral fat content when measured in a clinical trial investigating the efficacy of a product for weight loss. Rather, it can be a means to confirm that

reductions in waist circumference following treatment with a weight-management product are associated with the expected improvements in metabolic parameters.

It is likely that a large portion of study subjects will be taking concomitant medications to treat weight-related comorbidities such as hypertension, type 2 diabetes, and dyslipidemia. Since weight loss is expected to improve these comorbidities, an important secondary efficacy endpoint should be the proportion of subjects treated with the weight-management product compared with placebo who have a meaningful dose-reduction or complete withdrawal of their concomitant medication. Algorithms that direct dose reduction or withdrawal of concomitant medications based on changes in levels of blood pressure, lipids, or glycemia should be included in the study protocols.

Measures of quality of life from validated instruments also can be appropriate secondary efficacy endpoints.

c. Efficacy benchmarks

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- 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

- 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

Improvements in blood pressure, lipids, glycemia, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidites should be factored into the efficacy assessment of investigational weight-management products.

4. Standard of Care and Concomitant Medication

Overweight and obese patients enrolled in clinical studies of investigational weight-management products should receive standard of care, including medication, for comorbidities such as hypertension, dyslipidemia, and glycemic control.

5. Patients with Type 2 Diabetes

Compared with nondiabetic patients, overweight and obese patients with type 2 diabetes often respond less favorably to weight-management products and may face unique safety issues such as risk for sulfonylurea-induced hypoglycemia following weight loss (if the dose of sulfonylurea is not appropriately lowered or the drug discontinued). Therefore, sponsors should consider examining the efficacy and safety of weight-management products in trials dedicated to patients

with type 2 diabetes. The following recommendations should be considered when designing such trials:

- In general, patients should have baseline HbA1c levels between 8 percent and 10 percent.
- Patients should be excluded if they have fasting glucose levels greater than 270 mg/dl.
- Protocols should include escape criteria for poor glycemic control.
- Protocols should include an algorithm for the 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).
- Patient randomization should be stratified by baseline antidiabetic medication (e.g., metformin versus sulfonylurea versus a thiazolidinedione versus insulin) and baseline HbA1c level (e.g., less than or equal to 9 percent versus greater than 9 percent).
- Hypoglycemia safety should be monitored.[3]

C. General Safety Assessment of Weight-Management Products

To ensure that drug or biologic-induced weight loss is caused primarily by a reduction in fat content, not lean-body mass, a representative sample of study subjects should have a baseline and follow-up measurement of body composition by DEXA, or a suitable alternative.

In addition to routine safety monitoring, it may be appropriate for the development programs of some weight-management products to have specialized safety assessments. For example, products that directly interact with the 5HT receptor system, specifically the $5HT_2$ receptor subtypes, probably should include evaluation of risk for cardiac valvulopathy using serial echocardiography. The development plans for centrally acting weight-management products generally should include validated assessments of neuropsychiatric function.

Assessment of the immunogenic potential of therapeutic proteins should be performed over a period of at least 6 to 12 months. If adverse events characteristic of allergic or immunologic reactions are identified, the FDA may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of an application for registration or may be conducted after approval as a postmarketing commitment, based on the overall analysis of the product's risks and benefits. The appropriate timing of such studies can be discussed with the FDA at a pre-biologics license application meeting or other similar advice meeting.

For centrally acting weight-management products, sponsors should anticipate the need to conduct preclinical and clinical studies of abuse liability. Sponsors are encouraged to discuss the design of these studies with members of CDER's Controlled Substance Staff during the early phases of product development.

[3] Defining and Reporting Hypoglycemia in Diabetes: A Report from the American Diabetes Association Workgroup on Hypoglycemia, 2005, *Diabetes Care*, 28(5): 1245-9.

The need for and details of specific safety monitoring may change as new data emerge. Sponsors are encouraged to discuss their plans for specific safety monitoring with the division during the early stages of product development.

D. Weight-Management Products Used in Combination

Two or more products may be combined into a single fixed-dosed combination when each component makes a contribution to the claimed effect or effects (21 CFR 300.50).

Before initiating long-term clinical studies with fixed-dose combinations, sponsors should conduct the appropriate preclinical and pharmacokinetics studies. (See the guidances for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* and *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*.)

We recommend that the efficacy and safety of fixed-dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-management effects of the products. We have not defined a minimum difference in weight loss between a fixed-dose combination and its individual component products that should be achieved for the combination to be considered more efficacious than either of its components when used alone. However, a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss.

Once a fixed-dose combination has been deemed more effective than its individual components, the combination can then be examined versus placebo in phase 3 trials. This approach may preclude the need to include treatment groups for the individual components of the fixed-dose combination product in late-stage preapproval trials.

The efficacy of a product combination for weight management generally will be assessed using the same factors as those applied to a single product, as defined in section IV.B.3.

E. Weight-Management Products for Patients with Medication-Induced Weight Gain

A number of drugs, notably psychotropic and some anticonvulsant agents, are associated with moderate-to-marked weight gain (Baptista and Zarate et al. 2004; Pierre and Picard 2001). In addition to increasing the risk for adverse health outcomes, medication-induced weight gain may reduce compliance with the drug responsible for the increased body weight.

Before initiating long-term clinical studies in patients with medication-induced weight gain, sponsors should rule out clinically significant drug-drug interactions and perform appropriate preclinical toxicological studies of the subject products. For details, see the guidances for industry *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and*

Recommendations for Dosing and Labeling, and *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

Patients eligible for participation in trials examining the efficacy and safety of products for the treatment of medication-induced weight gain should have a documented increase in body weight of at least 5 percent within 6 months of starting a drug known to cause weight gain. Patients should have BMIs greater than or equal to 27 kg/m^2 with comorbidities or greater than or equal to 30 kg/m^2 with or without comorbidities at the time of screening.

Because most weight-management products act within the central nervous system (CNS) and many of the drugs commonly associated with moderate-to-marked weight gain are used to treat psychiatric or neurological disorders, unique issues of efficacy and safety may arise in studies of products used to treat medication-induced weight gain. For example, it would be important to demonstrate that the efficacy and safety of the medication causing the weight gain (e.g., atypical antipsychotic) was not adversely affected by a weight-management product with a CNS mechanism of action, and vice versa. These and similar issues should be taken into account when designing and determining the sample size of trials for the treatment of medication-induced weight gain.

The efficacy of a product for the treatment of medication-induced weight gain generally will be assessed using the same factors as those for weight management, as defined in section IV.B.3.

Serotonin syndrome, a potentially life-threatening condition characterized by akathisia, tremor, altered mental status, clonus, muscular hypertonicity, and hyperthermia (Boyer and Shannon 2005), has been observed in patients exposed to a single or two or more proserotonergic agents used in combination. Therefore, in general, weight-management products that act as agonists at serotonin receptors, particularly the $5\text{-}HT2_A$ subtype, should not be studied in combination with proserotonergic medications associated with weight gain.

Because of issues related to safety and possibly efficacy that are unique to the particular combinations of drugs studied, approval of a product for weight management in patients with medication-induced weight gain generally will be limited to the weight-inducing drug studied and will not apply to the drug class in which the compound is a member. For example, if a weight-management product is shown to be effective and reasonably safe in the treatment of clozapine-induced weight gain, the approved indication would be limited to clozapine-induced weight gain and would not necessarily apply to the entire class of atypical or second generation antipsychotics.

V. CLINICAL ASSESSMENT OF LONG-TERM WEIGHT-MANAGEMENT PRODUCTS IN PEDIATRIC PATIENTS[4]

Because the benefit of weight-management products should be carefully weighed against potential toxicity, particularly in the pediatric population, we anticipate that phase 3 data in adults generally will be available before a new product is studied in children.

To ensure that the most appropriate dose or doses are studied in phase 3 trials, an assessment of the pharmacokinetics of a weight-management product in pediatric patients may be appropriate before initiation of long-term clinical studies. Pharmacokinetics and dose-ranging studies generally should include patients with age- and sex-matched BMIs greater than or equal to the 95th percentile.

Trials examining the efficacy and safety of a weight-management product in pediatric patients should be randomized, double-blind, placebo-controlled, and 1 year in duration. We suggest that initial pediatric studies be limited to adolescents (i.e., 12 to 16 year olds). Eligible patients should have age- and sex-matched BMIs greater than or equal to the 95th percentile (see http://www.cdc.gov/growthcharts). Patients should have a documented history of failing to lose sufficient weight with lifestyle modification before enrollment into studies of a weight-management product.

We recommend that initial clinical studies include patients with one or more weight-related comorbidities such as type 2 diabetes, dyslipidemia, or hypertension. Once a satisfactory risk-benefit profile has been established in this high-risk group of patients, studies of lower risk patients can be considered. Effort should be made to recruit equal numbers of males and females and representative samples of patients from ethnic groups in which the prevalence of obesity is high.

The lifestyle modification program should continue following randomization to product or placebo and its importance emphasized at appropriate intervals throughout the trials.

Because linear growth should be taken into account when assessing changes in the body weight of children and adolescents, the primary efficacy parameter in weight-management trials of pediatric patients should be a function of the change in BMI (e.g., the mean percent change in BMI and the proportion of patients who lose greater than or equal to 5 percent of baseline BMI). Height measurements should be obtained from a wall-mounted stadiometer.

Since demonstration of adequate safety necessitates a larger sample size than demonstration of efficacy, we anticipate that the sample size of the long-term pediatric weight-management studies will be determined by considerations of the product's mechanism of action and safety profile in adults. Sponsors should discuss and justify their proposed sample size with the division before initiating the study.

[4] For details on preclinical and pharmacokinetic evaluations for pediatric product development, see the ICH guidances for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceutics* and *E11 Clinical Investigation of Medicinal Products in the Pediatric Population.*

In addition to standard safety evaluations specific to growing children (e.g., assessing Tanner stage at baseline and endpoint), studies of centrally acting weight-management products in pediatric patients also should include validated assessments of neuropsychiatric function. Other specialized safety assessments may be appropriate depending on the product's mechanism of action and its safety profile in adults.

The efficacy assessment of a weight-management product in pediatric patients will take into account the product's effectiveness in overweight and obese adults as well as the magnitude of the difference in the mean and categorical (greater than or equal to 5 percent) changes in BMI from baseline to Year 1 in pediatric patients treated with active product versus placebo.

VI. STATISTICAL CONSIDERATIONS

A. Sample Size

The number of subjects in a placebo-controlled trial should be the maximum of sample sizes calculated based on the co-primary endpoints of categorical response defined as greater than or equal to 5 percent reduction in baseline body weight after 1 year, and change from baseline weight. Calculations should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes for the calculations should represent clinically meaningful differences.

B. Preventing Missing Data from Premature Subject Withdrawal

Historically, there have been high rates of premature subject withdrawal in long-term trials of weight-management products. To allow for a true intent-to-treat (ITT) analysis, we encourage sponsors to obtain body weight measurements in all subjects who prematurely withdraw from late-stage preapproval trials near the calendar date at which they were scheduled to complete the trial (Simons-Morton and Obarzanek et al. 2006). For example, a subject who withdraws from a 12-month study after 6 months of treatment should have a body weight measurement at the time he or she would have completed 12 months of study participation.

C. Analysis Methods

Response rates should be compared between treatment groups using statistical methods appropriate for categorical data. A sensitivity analysis should be conducted that considers subjects who are treated, drop out, and do not have complete post-baseline data as treatment failures.

The analysis of (percentage) weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model. The analysis should be applied to the last observation carried forward on treatment in the modified ITT population defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. The imputation strategy should always be prespecified and should

consider the expected dropout patterns and the time-course of weight changes in the treatment groups. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. Repeated measures analyses can be used to analyze longitudinal weight measurements but should estimate the treatment effect at the final time point. Statistical models should incorporate as factors any variables used to stratify the randomization. As important as assessing statistical significance is estimating the size of the treatment effect. If statistical significance is achieved on the co-primary endpoints, type 1 error should be controlled across all clinically relevant secondary efficacy endpoints intended for product labeling.

D. Graphical Methods

Graphical methods showing treatment effects over time for completers should be presented. Cumulative distribution plots can be useful for showing response rates for different definitions of response based on the percentage of subjects with a change value equal to or less than the value on the x-axis selected to define the positive response. Additional graphical presentations of the data to illustrate the effect of the drug are encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

VII. LABELING CONSIDERATIONS

Data on the changes in the major weight-related comorbidities are important in assessing the overall risk-benefit profile of a new weight-management product and can be included in the Clinical Studies section of the product's labeling. However, it is important to recognize that even though secondary efficacy endpoints are prespecified and the overall type 1 error rate is controlled for, that does not necessarily guarantee that all secondary endpoints will be included in labeling if the differences between active-product and placebo-treated groups are of nominal statistical significance. The clinical significance and consistency across studies of any observed differences will be important in determining whether the secondary efficacy data merit inclusion in the Clinical Studies section of the labeling.

VIII. STAND-ALONE INDICATIONS FOR THE PREVENTION OR TREATMENT OF WEIGHT-RELATED COMORBIDITIES

As mentioned earlier, weight loss through lifestyle modification is associated with improvements in blood pressure, lipid levels, glucose and insulin metabolism, and other physiometabolic endpoints. Improvements in these comorbidites are expected following drug or biologic-induced weight loss, and from a regulatory perspective, they are considered part of the weight-management indication. Thus, for a weight-management product to obtain a stand-alone indication for the prevention or treatment of type 2 diabetes, dyslipidemia, hypertension, or any other weight-related comorbidity, it should be shown that the product effectively prevents or treats the comorbidity through a mechanism that is independent of weight loss.

IX. METABOLIC SYNDROME

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. The FDA does not necessarily consider the metabolic syndrome to represent a distinct disease entity. At present, there is no single etiological factor or central pathogenetic abnormality identified as mediating the constellation of excess visceral adiposity, abnormal lipids, elevated blood pressure, and insulin resistance that comprise the metabolic syndrome. Nonetheless, in addition to lifestyle modification, a host of drug therapies now exist to address individual or multiple components of the syndrome (e.g., lipid altering agents, antihypertensives, insulin sensitizers). Ideally, a therapeutic product intended to treat metabolic syndrome should *normalize* or improve all components of the syndrome, independent of weight loss (see section VIII), and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality.

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