CONTRAVE (NALTREXONE SR/BUPROPION SR COMBINATION)

ADVISORY COMMITTEE BRIEFING DOCUMENT

NDA 200063

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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EXECUTIVE SUMMARY

INTRODUCTION

This document summarizes data in support of the approval of Contrave, a novel combination product for the treatment of obesity composed of bupropion and naltrexone developed by Orexigen, Inc. of La Jolla, California.

Proposed Indication: The treatment of obesity and weight management, including weight loss and maintenance of weight loss, 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).

Proposed Dosing: The recommended daily dose of Contrave is two 8 mg naltrexone/90 mg bupropion (8/90) tablets taken twice daily for a total daily dose of 32 mg naltrexone/360 mg bupropion (32/360). Upon initiation, Contrave dosing should be escalated starting with one tablet taken daily for the first week, followed by the addition of another tablet each day during each subsequent week, until the total daily maintenance dose of two tablets twice a day (32/360) is reached at the start of Week 4.

Additional Labeling Considerations: Most patients who respond to Contrave will have done so by 4 months of treatment. If a patient has not exhibited clinically meaningful weight loss (e.g., at least 5%) after 4 months of treatment, the physician should consider discontinuation of Contrave and initiation of other weight management strategies should be considered. Patients may experience elevated blood pressure or pulse during Contrave treatment; the risk may be greater during the initial 3 months of therapy. If clinically relevant and sustained (e.g., at least two consecutive measurements) increases in blood pressure or pulse occur, Contrave should be discontinued. As patients with hypertension or a history of hypertension may be at increased risk of blood pressure elevations, care should be exercised when initiating treatment with Contrave in such patients.

Regulatory and FDA Guidance Considerations: The Contrave clinical development program was conducted in the framework of the requirements set forth in the 2007 FDA Guidance on developing products for weight management, with respect to appropriate patient exposure and study duration, and inclusion of patients with various comorbidities. According to the guidance, demonstration of efficacy after 1 year of treatment can be achieved by meeting *either* of the following co-primary endpoints:

- The difference in mean weight loss between the active treatment group and placebo is at least 5% and the difference is statistically significant.
- The proportion of patients who lose ≥5% of their baseline body weight in the active treatment group is at least 35%, is approximately double the proportion in the placebo group, and the difference between the active and placebo groups is statistically significant.

All four Phase 3 studies showed statistically significant improvement in each co-primary endpoint relative to placebo. Contrave met the second benchmark for weight loss efficacy in three of the four studies. Achieving 5% weight loss is not only an FDA guidance efficacy benchmark, but this degree of weight loss is known to confer significant cardiometabolic

benefit. Similarly, the Contrave trials demonstrated beneficial effects on prespecified weight-related cardiometabolic parameters, including:

- waist circumference,
- triglycerides, HDL-cholesterol,
- high-sensitivity C-reactive protein (hs-CRP),
- glycemic control (fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance [HOMA-IR], and, in patients with diabetes, hemoglobin A_{1c} [HbA_{1c}]),
- quality of life and control of eating.

Consistent with the known pressor effect of bupropion, NB-treated patients experienced increases in blood pressure and heart rate compared to placebo, although reduction in weight was associated with reduction in mean blood pressure in both treatment groups. Across all of the secondary manifestations of the illness of obesity, the greatest benefits of Contrave are likely in patients who achieve and maintain at least a 5% reduction in body weight.

In addition to the FDA guidance, the clinical development program was informed by various interactions between Orexigen and the Agency, including End-of-Phase 2 (EOP2) and pre-New Drug Application (pre-NDA) meetings. Key elements of the development program influenced by these interactions include:

- The adequacy of Study NB-201 to satisfy the regulatory requirements for a fixed-dose combination product.
- Details of the prospective statistical analysis plans for the four Phase 3 studies.
- Use of a prospective assessment of suicidality in the Phase 3 clinical trials, i.e., the Inventory of Depressive Symptomatology-Self Reported (IDS-SR), together with an assessment using the Columbia Classification Algorithm of Suicide Assessment (C-CASA)
- The design and conduct of clinical drug-drug interaction (DDI) studies of Contrave with representative antihypertensive, anti-diabetic, and lipid-lowering medications.

BACKGROUND

Contrave (generally referred to as "NB" hereafter), a novel combination product for the treatment of obesity, is composed of bupropion (a relatively weak inhibitor of the neuronal uptake of norepinephrine [NE] and dopamine [DA]) combined with naltrexone (a mu-opioid receptor antagonist). Bupropion has been shown to stimulate hypothalamic pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (α-MSH) which, in turn, binds to melanocortin 4 (MC4) receptors. The binding of α-MSH to MC4 receptors initiates a cascade of actions that results in weight loss via reduced energy intake and increased energy expenditure (Cowley et al., 1999). When α-MSH is released, POMC neurons simultaneously release β-endorphin, an endogenous agonist of the mu-opioid receptor that mediates a negative feedback loop on POMC neurons leading to a decrease in the release of α-MSH (Cowley et al., 2001; Ibrahim et al., 2003; Kelly et al., 1990; Loose and Kelly, 1990). Blocking this inhibitory feedback loop with naltrexone is proposed to facilitate

a more potent and longer-lasting activation of POMC neurons, thereby amplifying effects on energy balance. As a result, co-administration of bupropion and naltrexone produces a substantially greater effect on the POMC firing rate than either compound administered alone, suggesting that the drugs act synergistically.

CLINICAL PERSPECTIVE ON OBESITY AND ITS TREATMENT

Obesity is a rapidly growing epidemic among adults, adolescents, and children in the United States. Currently, there are three main approaches to the treatment of obesity: (1) diet, physical activity, and behavioral modification (diet and exercise); (2) pharmacotherapy; and (3) surgery. Diet and exercise is the mainstay of weight management and generally precedes other measures. Unfortunately, diet and exercise alone yield mostly limited and transient weight loss, with many individuals finding it difficult to adhere to such regimens. The strategy to implement pharmacotherapeutic or surgical approaches in addition to diet and exercise depends upon the patient's BMI as well as the presence of obesity-related comorbidities. However, unlike the situation for other metabolic diseases such as hypertension and type 2 diabetes, there are very limited obesity pharmacotherapies available. Although orlistat is approved for long-term use and provides efficacy beyond that usually achievable using diet and exercise alone, it is not tolerated well by some patients. The other available pharmacotherapies, e.g. phentermine, are approved for short-term use only. While more invasive options (e.g., gastric banding, bariatric surgery) do result in greater weight loss than is achievable with pharmacotherapy, these are targeted primarily to those patients with the highest BMI. The benefit of surgery is also offset by greater expense and risk. In the face of such limited options, patients often resort to the use of off-label medications or dietary supplements that may be ineffective or unsafe. In this context, agents such as NB may offer viable alternatives for many obese patients.

NB CLINICAL DEVELOPMENT PROGRAM

The NB clinical development program comprised 23 completed trials, including 15 Phase 1, four Phase 2, and four pivotal Phase 3 studies. These 23 studies allowed for a thorough assessment of the safety, efficacy and pharmacokinetics (PK) of NB. Across the Phase 2 and Phase 3 studies, a total of 3475 patients were exposed to NB for a total of 2313 patient-years of exposure. Of the 3475 patients, nearly one-half (1661 patients; 47.8%) received NB for at least one year.

The 15 Phase 1 studies were conducted as part of the formulation development and clinical pharmacology programs. A number of these studies utilized crossover designs which accommodated multiple objectives (e.g., establishing both the effect of food on the PK of NB as well as investigating potential DDIs).

The Phase 2 program consisted of four studies, as summarized below:

- Two studies (OT-101 [a 24-week proof of concept study] and NB-201 [a 48-week study]) were conducted to examine the weight loss efficacy, safety and tolerability of the combination of naltrexone and bupropion compared with the individual components and placebo in obese patients. The results of these two studies informed the study design and doses of NB to evaluate in Phase 3.

- Two open-label studies were completed in special populations of overweight and obese patients (i.e., nicotine-dependent patients [NB-401] and patients who had major depression [NB-402]).

The Phase 3 program consisted of four large, 56-week, multicenter, randomized, double-blind, placebo-controlled studies (Studies NB-301, NB-302, NB-303, and NB-304) in obese and overweight patients. Across these studies the efficacy, safety and tolerability of NB were evaluated in three settings:

- In patients who received customary diet and behavioral counseling, including prescribed exercise (Studies NB-301 and NB-303).
- In patients who underwent intensive lifestyle modification counseling (Study NB-302).
- In patients who had type 2 diabetes (Study NB-304) and who received customary diet and behavioral counseling.

Studies NB-301, NB-302 and NB-303 enrolled a similar patient population (i.e., obese patients with either uncomplicated obesity, or obese/overweight patients with controlled hypertension and/or dyslipidemia). However, there were unique design elements associated with each of the studies (in addition to the unique enrollment of patients with type 2 diabetes in Study NB-304):

- Study NB-301 investigated two daily doses of NB: naltrexone 16 mg/day + bupropion 360 mg/day (NB16) and naltrexone 32 mg/day + bupropion 360 mg/day (NB32); NB32 was the primary dose investigated in all other Phase 3 studies (including NB-304). The study also evaluated the safety of abrupt versus tapered discontinuation of NB after 56 weeks of treatment.
- In Study NB-303, patients who did not experience or maintain at least 5% weight loss from baseline between Weeks 28-44 while on NB32 therapy were re-randomized to continue taking NB32 or increase their daily dose to NB48 (naltrexone 48 mg/day + bupropion 360 mg/day) to determine if the naltrexone dose increase resulted in additional weight loss. The study also evaluated two slightly different dose escalation schemes (3 weeks versus 4 weeks).
- Study NB-302 assessed the efficacy and safety of NB32 in patients undergoing an intensive behavioral modification program that included regular group counseling sessions, maintenance of food diaries, diet and exercise.

PHASE 3 EFFICACY RESULTS

Weight Loss at Endpoint. All four studies in the NB Phase 3 program demonstrated statistically significant and clinically meaningful weight loss following up to 56 weeks of treatment with NB32 (and NB16 in Study NB-301) compared with placebo, as shown in the table below. Percent weight loss from baseline and the percent of patients achieving at least 5% weight loss from baseline were similar between studies NB-301 and NB-303, reflecting their similar designs and populations. Study NB-302 patients exhibited greater weight loss on average in both the NB- and placebo-treated groups, consistent with the use of a more intensive behavioral modification regimen in that study. NB32-treated patients with type 2 diabetes in Study NB-304 showed the smallest degree of weight loss, although a significantly greater proportion of NB32-treated patients benefitted with at least 5% weight loss at endpoint compared to placebo. The average percent weight loss from baseline observed with NB treatment across the four studies corresponded to between approximately 5 and 9 kg (11 to 22 pounds).

Summary of Weight Loss Effects in the NB Phase 3 Clinical Studies

Study Mean Values[a]	**Placebo**	**NB32**[b]
NB-301, N	511	471
Baseline Body Weight (kg)	99.3	100.2
% Change from Baseline to Week 56	-1.3	-6.1
Difference from Placebo		-4.8
% Achieving ≥5% Decrease at Week 56	16.4	48.0
NB-303 (Week 28)[c], N	456	825
Baseline Body Weight (kg)	99.3	100.7
% Change from Baseline to Week 28	-1.9	-6.5
Difference from Placebo		-4.6
% Achieving ≥5% Decrease at Week 28	17.5	55.6
NB-303 (Week 56), N	456	702
Baseline Body Weight (kg)	99.3	100.2
% Change from Baseline to Week 56	-1.2	-6.4
Difference from Placebo		-5.2
% Achieving ≥5% Decrease at Week 56	17.1	50.5
NB-302, N	193	482
Baseline Body Weight (kg)	101.9	100.7
% Change from Baseline to Week 56	-5.1	-9.3
Difference from Placebo		-4.2
% Achieving ≥5% Decrease at Week 56	42.5	66.4
NB-304, N	159	265
Baseline Body Weight (kg)	105.0	106.4
% Change from Baseline to Week 56	-1.8	-5.0
Difference from Placebo		-3.3
% Achieving ≥5% Decrease at Week 56	18.9	44.5

[a] Analysis based on modified intent-to-treat population (patients with a baseline body weight measurement and at least one post-baseline measurement while on study drug) with last observation carried forward.
[b] All treatment comparisons were significantly different than placebo ($p<0.001$).
[c] Week 28 was the primary endpoint assessment for Study NB-303.

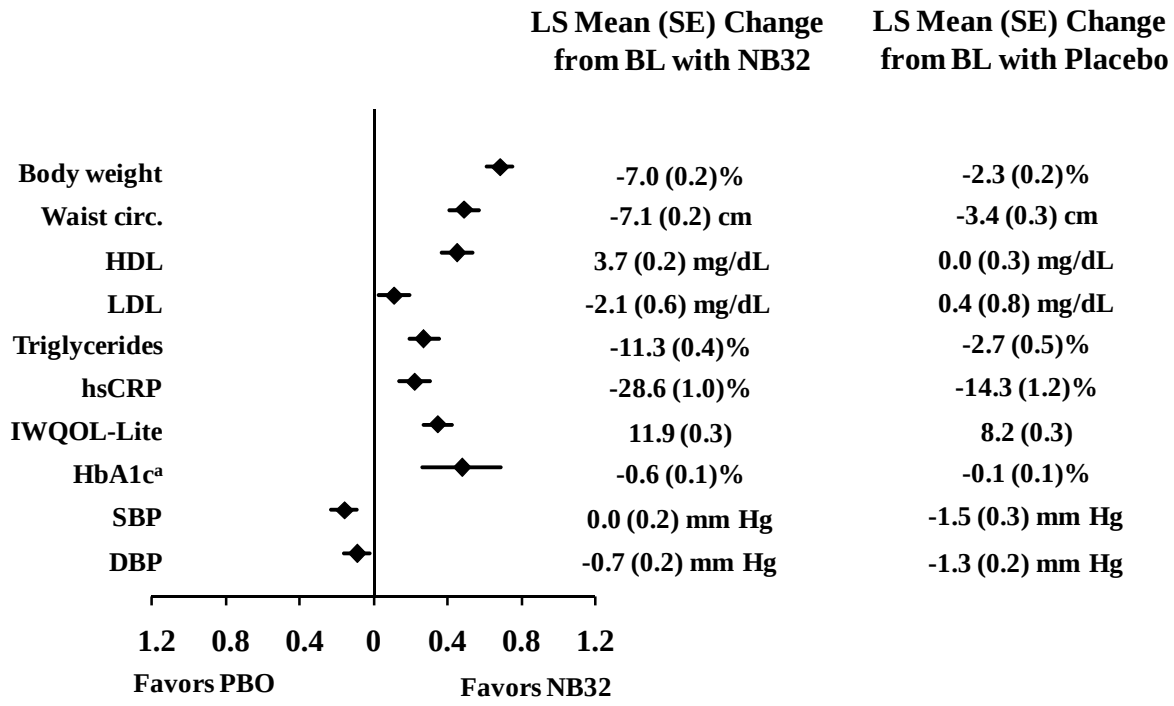
Sensitivity analyses conducted on the co-primary efficacy measures examined the robustness of the treatment effect. The statistically significant treatment effects observed on the primary analysis set following treatment with NB32 were also observed for each sensitivity analysis

employed, although the magnitude of the effect was in some cases attenuated relative to the primary analysis. These included analyses that were done to address potential bias introduced by patient discontinuations and assumed either zero weight loss (baseline observation carried forward [BOCF]) or weight regain following discontinuation of study drug (weight regain imputation method).

The weight loss efficacy of NB was observed across all demographic and clinical characteristics evaluated, including patients with hypertension, dyslipidemia, a history of cardiovascular (CV) disease, type 2 diabetes, impaired fasting glucose, or history of depression at baseline.

Weight-Related Cardiometabolic Parameters. Across the four Phase 3 studies, treatment with NB32 (and NB16 in Study NB-301) on average resulted in statistically significant and clinically meaningful improvements on multiple weight-related cardiometabolic parameters, including waist circumference, HDL-C, triglycerides, and hs-CRP, compared to placebo, as shown below in the plot of effect sizes.

Summary of Effects on Weight-Related Cardiometabolic Parameters in the NB Phase 3 Clinical Studies (Pooled Data)



[a] HbA1c is for NB-304 only; analysis based on modified intent-to-treat population
Data are effect size and associated 95% CI; For parameters where a negative treatment difference indicates improvement over placebo, the values are reversed so that the direction that favors NB32 remains constant.

Blood Pressure. Across the four Phase 3 studies, the mean changes from baseline to endpoint in systolic blood pressure (SBP) in NB32-treated patients were small (-1.3 to +0.6 mm Hg); similar mean changes from baseline to endpoint were observed in diastolic blood pressure (DBP; -1.4 to +0.4 mm Hg). Placebo-treated patients generally displayed greater mean decreases from baseline in blood pressure (-3.9 to -0.5 mm Hg for SBP and

-2.8 to +0.3 mm Hg for DBP) compared to NB-treated patients. In NB-treated patients, greater decreases in mean SBP and DBP were observed in those achieving ≥5% weight loss at Week 56 compared to those NB-treated patients who did not reduce weight by at least that amount. While placebo-treated patients had greater reductions in blood pressure when they achieved ≥5% weight loss, they were significantly less likely to achieve this degree of weight loss compared to NB-treated patients.

Glycemic Control. Results from Study NB-304 indicate that the effects of NB therapy on weight are also associated with clinically significant improvements in glycemic control in obese patients with type 2 diabetes mellitus.

- At Week 56, NB32-treated patients experienced a significant reduction of -0.63% in HbA1c compared with a -0.14% reduction in placebo-treated patients ($p<0.001$). In addition, a higher proportion of NB32-treated patients achieved HbA1c values <7% (44.1%) and <6.5% (21.0%) compared with placebo-treated patients (<7%: 26.3%, and <6.5%: 10.2%).
- A lower proportion of NB32-treated patients required the use of rescue medications (i.e., new antidiabetic medications added or existing medication doses increased) for glycemic control compared with placebo-treated patients (NB32: 22.3%; placebo: 35.2%; $p<0.01$).

As expected in obese and overweight patients losing clinically meaningful amounts of weight, in the three Phase 3 studies in patients without diabetes, greater improvements were observed in fasting glucose, fasting insulin, and HOMA-IR for NB-treated patients compared with placebo-treated patients.

Quality of Life. In each of the four pivotal studies, the Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire (Kolotkin et al., 2001) was a secondary endpoint to assess the effect of NB treatment on patients' self-reported overall quality of life. Weight loss following treatment with NB was associated with significant improvement in the IWQOL-Lite total score in 3 of the 4 Phase 3 studies (NB-301, NB-302 and NB-303). Improvements were also observed in various subscales, most consistently on the physical function and self-esteem subscales. Furthermore, NB32-treated patients in those three studies were more than twice as likely to achieve a clinically meaningful improvement, based on ad hoc analyses as described by Crosby et al. 2004, in their IWQOL-Lite total score relative to placebo-treated patients ($p<0.001$).

Control of Eating. The Control of Eating (COE) questionnaire is composed of 20 self-reported visual analog scales that explore subjective experiences that can influence food consumption. These include but are not limited to appetite, satiety, food cravings (in general and for specific items), and mood. The COE questionnaire was utilized as an exploratory tool in all four Phase 3 trials to examine the subjective patient experience during NB treatment. Item 19 ("Generally, how difficult has it been to control your eating?") may represent a summary measure of patient perception of eating control and was pre-specified in Studies NB-301, NB-303 and NB-304 based on results from Study NB-302. Greater effects of NB treatment were observed in multiple items across the four pivotal studies. The most consistent effects were observed in Item 19 of the COE questionnaire in addition to effects on other items related to decreasing hunger, increasing satiety, and increased ability to resist food cravings.

SAFETY

The safety profile of NB was well characterized in a large clinical program that included 3475 NB treated patients overall and 2313 patient-years of experience, using primarily the proposed NB32 and NB16 daily doses. Data were integrated (pooled) across the 24-week primary efficacy period of Phase 2 study NB-201 and the four 56-week Phase 3 studies (NB-301, NB-302, NB-303, and NB-304) to create the Primary Dataset (N=1515 placebo patients; N=3239 NB patients), as these studies were all placebo-controlled and 6- to 12-months in duration. The observed NB safety and tolerability profile was generally comparable to the well-established safety profiles associated with naltrexone and bupropion, each with more than 20 years of post-marketing experience and approximately 1 million and more than 50 million unique exposures, respectively.[1] The individual doses of naltrexone and bupropion in the NB combination were within or lower than the approved range of doses for the individual components. With the exception of nausea and vomiting, the NB combination of naltrexone and bupropion did not appear to be associated with increased adverse events (AEs) relative to the individual components.

Adverse Events. The most commonly reported AEs (those that occurred at a ≥5% incidence in the Total NB group and greater than the incidence in the placebo group) for patients treated with NB are displayed in the table below.

Treatment-emergent Adverse Events Occurring in ≥5% of the Total NB Group and Greater Than Placebo: Primary Dataset, Double-Blind Treatment Phase

MedDRA Preferred Term	Placebo (N=1515) n (%)		NB16 (N=633) n (%)		NB32 (N=2545) n (%)		Total NB (N=3239) n (%)	
Patients with any AE	**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%)
Dry mouth	35	(2.3%)	47	(7.4%)	205	(8.1%)	256	(7.9%)
Diarrhoea	79	(5.2%)	33	(5.2%)	180	(7.1%)	215	(6.6%)

The pattern of AEs in NB-treated obese patients with type 2 diabetes was generally similar to that of patients without diabetes, although the relative difference between the NB32 and placebo groups for AEs of nausea, vomiting, diarrhea, and hypertension was greater in patients with diabetes than in those without diabetes. The difference for nausea, diarrhea, and vomiting may be explained, in part, by concomitant medications (e.g., metformin) associated with gastrointestinal adverse effects, or interaction with diabetic gastroenteropathy. More patients with diabetes (62%) than patients without diabetes (approximately 20%) had

[1] Estimates Based on Wolters Kluwer Rx and Patient Data, Jan – Dec 2009 and IMS Health Rx and Persistence Data, Jan 1985 – Dec 2009.

baseline hypertension, as well as higher baseline mean blood pressure values in general. Relative to placebo, changes in blood pressure in patients with diabetes were generally similar to or less than that observed in patients without diabetes. Across other pre-defined subgroup analyses (ethnicity, race, sex, baseline smoking status, baseline antihypertensive medication, ≥5% weight loss at endpoint, and obesity class), no meaningful differences in the safety or tolerability profile of NB were observed.

Overall, AEs mostly occurred early in treatment, were generally mild or moderate in severity, and were self-limited. The most common AEs leading to discontinuation (nausea, headache, dizziness, vomiting, insomnia, anxiety, urticaria, and depression) were generally consistent with the commonly reported AEs overall. Serious AEs (SAEs) were infrequent (generally <0.1% for any given event) and with the exception of cholecystitis/cholelithiasis events, equally distributed across treatment groups.

Hemodynamic Effects. Consistent with the known hemodynamic effects of bupropion, NB treatment was associated with increases of approximately 1 mm Hg in mean SBP and DBP early (at weeks 4 and 8) in treatment. By week 12, mean blood pressure returned to baseline with subsequent reductions below baseline of approximately 1 mm Hg. Endpoint values were either unchanged or decreased relative to baseline values. Patients treated with placebo consistently experienced greater decreases in blood pressure. In placebo-treated patients, both mean SBP and DBP decreased from baseline over the course of the study and resulted in Week 56 values averaging 1-2 mm Hg below baseline. For both placebo- and NB-treated patients, greater weight loss was associated with greater decreases in mean blood pressure. The incidences of SBP and DBP increases above pre-specified values (e.g., SBP ≥140 mm Hg; DBP ≥90 mm) were higher in the Total NB group than the placebo group, as were the incidences of relative increases from baseline (SBP ≥10 mm Hg; DBP ≥5 mm Hg). Outlier values, however, were not usually sustained, and hypertension AEs were infrequent in both treatment groups.

Twenty-four hour SBP and DBP patterns were similar between NB32- and placebo-treated patients. The normal circadian variation of blood pressure, including a nocturnal decrease, was maintained in both treatment groups. This is particularly relevant as a loss of the nocturnal lowering in blood pressure is regarded as an important predictor of poor CV outcome.

Mean heart rate in the placebo group generally fluctuated from baseline by ±1 bpm, while mean heart rate in the Total NB group from Week 4 through Week 56 was increased above baseline by approximately 1-3 bpm with no apparent pattern over time. The occurrence of outlier values (e.g., ≥100 bpm or increase from baseline ≥10 bpm) was low and predominantly transient, occurring with a slightly greater frequency in NB-treated patients compared with placebo-treated patients. Twenty-four hour heart rate patterns were similar between treatment groups. Arrhythmia-type events occurred at a slightly higher incidence in NB-treated patients (5.5%) than in placebo-treated patients (4.2%). This difference was largely due to palpitations, with smaller increases noted for tachycardia and increased heart rate events. Importantly, no increase in syncope was observed and electrocardiogram (ECG) findings were similar between the treatment groups, with no treatment effect on QTc or other interval prolongations.

Major cardiovascular AEs (MACE) events were uncommon. MACE events occurred at comparable rates between the placebo (0.07%; 1 stroke) and NB32 (0.12%; 3 myocardial infarctions, including one death) groups. MACE with revascularization events were also similar between treatment groups (0.20% placebo and 0.16% NB32). The exposure-adjusted incidence rate of MACE events was approximately 0.2/100 patient-years, which is consistent with predicted rates for a female middle-aged obese population (Willett et al., 1995; Manson et al., 1990). The single death resulting from a presumed myocardial infarction occurred in an NB treated patient with multiple pre-treatment cardiovascular risk factors.

Seizures. Adverse events of seizure occurred in 2 NB-treated patients (incidence <0.1%) and none in placebo, which is consistent with what has been previously described with bupropion monotherapy (0.1% with doses up to 300 mg).

Depression and Suicidality. Adverse events related to depression occurred less frequently in NB-treated patients (2.8%) than placebo patients (3.4%). Based on the C-CASA categorization, there were no completed suicides, suicide attempts, or preparatory acts towards imminent suicidal behavior in any treatment group. The incidence of suicidality was <0.1% (1 patient) in the Total NB group compared with 0.2% (3 patients) in the placebo group, suggesting there is no increased risk for suicidal behavior with NB treatment.

Hepatotoxicity and Biliary Effects. No changes in liver function tests were observed in the NB clinical studies, consistent with the naltrexone dose in NB being less than those associated with hepatotoxicity. Although there was a higher incidence of cholecystitis observed in association with NB therapy compared with placebo, this effect was likely a consequence of weight loss combined with the known higher inherent risk for this population.

Other Safety Findings. Despite the requirement for all female patients of child bearing potential to use birth control, 21 (0.78%) women treated with NB and 7 (0.56%) women treated with placebo became pregnant. There were no reports of congenital anomalies.

There were no other clinically significant changes in physical examinations or laboratory findings. Pre-specified safety topics of special interest occurred with a frequency and severity expected for the treatment population or else consistent with the known safety profile of the approved NB constituents.

RISK MANAGEMENT

Risk Evaluation and Mitigation Strategy (REMS). Orexigen is proposing a risk mitigation plan to address the potential serious risks of NB therapy. The foundation of this plan is a REMS reinforced through elements of the product launch program to facilitate the appropriate use of NB.

The specific objectives to be achieved by the REMS are to inform and educate Healthcare Professionals (HCPs) and patients about the following:

- The potential serious risks associated with the use of NB including:
    - Suicidality thinking and behavior (based on established risk mitigation strategies for marketed bupropion).
    - Seizures (based on established risk mitigation strategies for marketed bupropion).

  - Serious cardiovascular effects (as a result of the known effect of bupropion on blood pressure and heart rate).
- The importance of appropriate patient selection:
  - BMI ≥30 or ≥27 kg/m^2 in patients with comorbidities.
  - Exclusion of, or caution in patients with risk factors for the noted serious risks
- The importance of appropriate and safe use of NB, specifically:
  - Appropriate dosing and dose escalation.
  - Guidance regarding periodic assessments of blood pressure and weight.

The REMS has been designed to communicate information to HCPs and patients by means of a Medication Guide and Communication Plan. The communication plan will include:

- A Dear HCP letter that will be mailed to HCPs most likely to prescribe NB. The letter is designed to convey and reinforce the potential serious risks associated with the use of NB. This letter will also reinforce safe use procedures for NB.
- An education program will include a NB Healthcare Professional Education Program Kit, which will contain HCP and patient labeling, a patient treatment algorithm, and a physician-patient counseling guide.

All REMS materials will be tested prior to their first use and then serially evaluated by a combination of knowledge, attitude and behavior surveys, chart reviews and/or a representative survey of anonymized patient electronic records to assess:

- Physician and patient comprehension of REMS materials
- Adherence to REMS recommendations
- Outcomes associated with NB therapy, including weight change (as available) and targeted AEs

Appropriate Use Program (AUP). The AUP is designed to complement the REMS by supporting accurate patient selection by clinicians, providing evaluation of medication effectiveness, assisting with treatment discontinuation among non-responders, and providing monitoring and support tools throughout the duration of care. To achieve these goals, education for appropriate and informed use will be integrated throughout all manufacturer-supported communications and will be accompanied by clinical tools designed for practical use at the individual HCP and patient levels. Program objectives include disease state education, NB appropriate use education, and a continuous support program for physicians, caregivers, and patients.

Patient Selection Considerations. As noted earlier, appropriate patient selection based on body composition, presence of comorbidities, and presence of specific risk factors will be a key element of safe use of NB. Analyses have been conducted to help define which patients may be more likely to benefit from continued treatment, versus those that might be identified early in their therapeutic trial as candidates for discontinuation of therapy. Specifically, as shown in detail below, early weight loss predicts long-term clinically meaningful weight loss. Similarly the presence of early blood pressure outlier values predicts later occurrence of blood pressure elevations. Therefore, monitoring for significant weight response (i.e., ≥5% early in treatment) as well as blood pressure outliers may provide important information to prescribers regarding whether to continue NB treatment.

- **Early Weight Loss as a Predictor of Long-Term Weight Loss.** Analyses were conducted to evaluate whether earlier weight loss (Weeks 4-28) is predictive of a 5% or greater weight loss response at week 56. Based on receiver operating characteristic curves 5% weight loss from baseline at Week 16 showed 75 to 85% accuracy in the four Phase 3 trials in identifying 5% responders at Week 56 with fair balance between sensitivity and specificity. Additionally, in a pooled analysis of the four Phase 3 trials, among the NB32 subjects who achieved ≥5% weight loss at Week 56 based on LOCF, more than 85% reached the responder status by Week 16.
- **Mitigation of Potential Risk Associated With Increased Blood Pressure and Heart Rate.** Odds ratios based on logistic modeling were used to assess whether the occurrence of late outliers (Weeks 28-56) of blood pressure and heart rate could be predicted based on the occurrence of early outliers (Weeks 4-16). For this assessment outliers were defined as at least 2 consecutive increases in the vital sign parameter ≥10 units relative to baseline during the early and/or late time period. Patients with an earlier SBP outlier had at least 12 times the odds of having outlier values late in treatment, compared to those without early outliers. Similar findings were noted for DBP and heart rate.

Other Risk Mitigation Considerations. Because both components of NB have been used individually in a large number of patients, many of whom share similar characteristics with patients who may seek weight loss treatments such as NB, it is unlikely that unforeseen risks will emerge as a result of the use of NB. Nonetheless, rigorous risk mitigation strategies as outlined earlier, in addition to routine pharmacovigilance with targeted surveillance and data collection for events of interest, will facilitate the monitoring and management of any unforeseen risks that could potentially occur.

In addition to the basic REMS elements and pharmacovigilance activities, Orexigen is developing a strategy to better assess potential cardiovascular risks of using NB. This includes the collection of real-time prescription and patient outcome data, as well as specific investigation to assess cardiovascular outcomes in a large real-world setting; these strategies are currently under development in discussion with the Agency.

In summary, the safe use of NB is considered readily achievable via appropriate patient selection, informed prescribing, appropriate patient care, and consideration of prompt discontinuation of treatment for patients who do not lose at least 5% of their body weight by 4 months into their treatment trial, or experience persistent, clinically significant elevations in blood pressure or heart rate.

Clinical Outcomes Assessment. The risks identified during the NB clinical development program can be managed in real-world clinical practice through labeling and risk management measures obtained post approval. However, assessing the risk of major adverse cardiovascular events (MACE) when the background rate is low (as is the case in the target population for NB treatment) presents significant challenges. One approach to facilitate event collection is to conduct a study in an enriched, high-risk subset of the overall population intended for treatment. An example of such an approach would be to assess potential cardiovascular risk associated with the use of antidiabetic agents in patients with type 2 diabetes, an inherently higher risk population. However, this approach may not be appropriate for evaluation of risk associated with obesity therapies because the intended

study population would generally not include higher risk patients (e.g., those with existing cardiovascular disease).

An alternative approach is to enroll a large number of patients from the intended lower-risk population. This approach has the advantage of providing results that are directly applicable and relevant to real-world use. The focus of such an investigation would be specific assessment of MACE, including myocardial infarction, stroke, acute revascularization and cardiovascular death. As previously noted, the low background rate necessitates a large sample size to reliably assess the frequency of these events, the exact sample size is dependent on the amount of excess risk to be ruled out.

With these considerations in mind, two alternative approaches for gathering large samples are being evaluated:

- A randomized interventional trial
- A prospective, longitudinal, comparative cohort

Orexigen has engaged an external advisory group from academia and industry to further develop appropriate plans. Orexigen intends to discuss these issues with FDA and reach agreement on an appropriate and feasible approach to a definitive and timely investigation of cardiovascular outcomes with Contrave use.

BENEFIT/RISK

Key benefits following treatment with NB are summarized below:

- Clinically meaningful weight loss was apparent early in treatment, and was greater than that observed with either naltrexone or bupropion alone. Weight loss was on average sustained, and those patients who continued treatment through 56 weeks experienced the most substantial weight loss. The efficacy of NB was observed across all demographic and clinical subgroups evaluated, including patients with hypertension, dyslipidemia, history of cardiovascular disease, type 2 diabetes, impaired fasting glucose, or history of depression.
- Significant effects of NB treatment were observed on a number of weight-related cardiometabolic parameters (e.g., waist circumference, triglycerides, HDL-cholesterol, and hs-CRP); HDL increases and triglyceride reductions were observed irrespective of history of dyslipidemia or treatment for this condition.
- Patients with type 2 diabetes benefitted from weight loss, improvements in waist circumference, HDL and triglycerides, and clinically significant improvements in glycemic control (particularly decreased HbA_{1c}). A lower proportion of NB-treated patients required adjustments to their antidiabetic medications due to poor glycemic control.
- Greater proportions of NB-treated patients reported clinically meaningful improvements in weight-related quality of life compared with placebo, providing further evidence of the range of clinical benefits that can be derived from NB treatment.
- Greater effects of NB treatment were observed on multiple items of the COE questionnaire.

Key safety findings from the NB development program include the following:

- The use of NB was generally well-tolerated, with the frequency and distribution of safety findings being consistent with the established profiles for naltrexone and bupropion.
- Common AEs such as nausea and vomiting tended to occur early in treatment (during the dose-escalation phase), were mostly mild to moderate in severity, and were generally self-limiting.
- The incidence of treatment-emergent SAEs overall was low; the vast majority of SAEs in NB-treated patients were considered unrelated to study drug.
- Initiation of treatment with NB was associated with transient increases from baseline of approximately 1 mm Hg in mean blood pressure, followed by small reductions below baseline. These increases are consistent with the known hemodynamic effects of bupropion and were attenuated by weight loss in patients who responded to therapy, although mean blood pressure reductions with NB were always less than that observed with comparable placebo patients. The small elevations in heart rate seen with NB treatment (compared with decreases with placebo) are also consistent with known bupropion effects.
- The hemodynamic effects of NB are due to bupropion. Bupropion has been extensively prescribed since its original approval more than 20 years ago, and has a long history of safe use even in populations considered at risk for CV disease.
- The incidence of major cardiovascular events (cardiovascular death, myocardial infarction and cerebrovascular accident) and revascularization procedures were low and comparable between NB- and placebo-treated patients, although the number of events is too low to draw firm conclusions.
- Seizures occurred infrequently at a rate that is consistent with that observed for the lowest approved dose of bupropion SR.
- Treatment with NB in the target patient population does not appear to be associated with an increased risk for depression or suicidality.
- No hepatotoxicity was observed with long-term NB treatment.
- Clinical laboratory evaluations were generally unremarkable, and values outside of normal ranges tended to be sporadic and unrelated to dose.
- Neither bupropion nor naltrexone has historically been associated with prolongation of QTc intervals, and review of QT, QTc and the other ECG parameters in patients during long-term NB treatment revealed no noteworthy findings.

In summary, the benefits of NB outweigh the risks given the clinically meaningful weight loss and improvement in multiple markers of cardiometabolic risk and patient-reported quality of life. These benefits in aggregate are expected to be greater in general clinical practice, as proposed labeling would lead to discontinuation of treatment for patients not experiencing at least a 5% decrease from baseline in body weight. Benefits are observed across a range of overweight and obese patient subgroups and in various treatment settings. Of note, the population of patients receiving currently approved bupropion-containing

therapies has important similarities to patients enrolled in the NB clinical program, as well as the population of patients who receive currently marketed obesity pharmacotherapy. In addition, clinical experience and investigation in relevant patient populations, including those with cardiovascular risk factors or established cardiovascular disease, have not identified specific safety signals for clinical cardiovascular events. Overall, the NB safety profile is well-understood, with known risks that are predictable and manageable via appropriate risk mitigation approaches. Orexigen is developing a plan for additional clinical studies to assess: 1) prescription utilization patterns, 2) physician and patient adherence to labeling, and 3) the impact of Contrave on cardiovascular outcomes. Discussion of study options with FDA is anticipated prior to the Advisory Committee.

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1 INTRODUCTION

1.1 Unmet Medical Need

Obesity, a serious medical condition resulting from an excess of body fat, is usually defined as a body mass index (BMI) ≥30 kg/m^2. Obesity results from an energy imbalance in which an individual consumes more calories than he or she expends over an extended period. The cause of obesity can be attributed to a number of genetic, environmental, and behavioral factors. High-calorie, sugary and fatty foods are generally pleasurable to consume, inexpensive and readily available. Furthermore, many individuals have a sedentary lifestyle which, when combined with an unhealthy, high-calorie diet, leads to obesity.

Obesity is a fast-growing epidemic among adults in the United States (U.S.), and the currently available therapeutic options have demonstrated limited success or, in the case of bariatric surgery, can be associated with complications including mortality (National Center for Health Statistics, 2010). There are very few approved pharmacological treatments for obesity and the unmet medical need continues to grow. The prevalence of obesity is high in the U.S., having reached approximately 32% in men and 36% in women (Flegal et al., 2010). In 2009, >20% of the population in 49 of the 50 states was obese while, as recently as 1995, no states met the obesity criterion (Behavioral Risk Factor Surveillance System, CDC). According to a World Health Organization (WHO) 2009 report on global health risks, diet-related risks and physical inactivity accounted for 25% of deaths in high income countries and 19% of deaths worldwide, based on 2004 data (WHO, 2009); up to 300,000 of these annual deaths occurred in the U.S. (Allison et al., 1999). Obesity tends to disproportionally affect lower socioeconomic groups and minorities, and the condition is associated with significant socioeconomic consequences (Enzi 1994; Averett and Korenman, 1999).

A number of medical conditions are exacerbated with increasing BMI, including diabetes, dyslipidemia, hypertension, impaired quality of life, and coronary heart disease (National Heart, Lung, and Blood Institute [NHLBI] Clinical Guidelines, 1998; Luppino et al., 2010). For example, there is over a 3-fold higher likelihood of death due to diabetes and over a 2-fold higher likelihood of death due to hypertension in obese individuals compared with otherwise healthy individuals with the same conditions (Wei et al., 1999). Even overweight individuals (25 kg/m^2 ≤ BMI <30 kg/m^2) share many of the same risks for morbidity and disability with the obese (Peytremann-Bridevaux and Santos-Eggimann, 2008).

In addition to the negative consequences obesity has on physical well-being, social stigmatization, discrimination and bias against obese persons are pervasive; in fact, many people view obesity as a personal failure as opposed to a true medical condition. The psychosocial impact of obesity poses numerous consequences for patients' self-esteem and psychological health, impacting their overall quality of life (Puhl and Heuer, 2010).

Obesity also places a significant burden on society in general as a result of increased healthcare utilization costs incurred by the obese population. The average medical costs for an obese individual are estimated to be 42% higher compared to an individual with normal weight (Finkelstein et al., 2009). In 2009 alone, obese individuals in the U.S. accounted for $147 billion worth of healthcare expenses (Finkelstein et al., 2009); by 2018, when it is estimated that 103 million Americans will be obese, this cost is projected to be $344 billion (http://www.americashealthrankings.org/2009/report/Cost%20Obesity%20Report-final.pdf).

The obesity epidemic also has a negative impact on the workplace, where it is estimated that $73 billion are lost annually due to an obesity-related decrease in workplace productivity (Finkelstein et al., 2010).

Weight loss that accompanies low-fat diets, exercise and pharmacological treatment has been shown to reduce the risk of type 2 diabetes mellitus, may be beneficial in cardiovascular (CV) disease, and may reduce mortality (Avenell et al., 2004). Modest weight loss starting at 4.5 kg is associated with decreased cardiovascular morbidity (Eilat-Adar et al., 2005), and in overweight and obese individuals (particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes), long-term weight loss of ≥5% following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis et al., 2005). In the 12-year follow-up portion of the U.S. Cancer Prevention Study, weight loss in individuals with type 2 diabetes resulted in a 25% reduction in total mortality and a 28% reduction in CV-related and diabetes-related mortality (Williamson et al., 2000). Intentional weight loss is known to result in an approximately 50% reduction in the risk of developing type 2 diabetes as well as lead to an improvement in multiple cardiometabolic risk factors (Diabetes Prevention Program Research Group, 2002). Furthermore, weight loss is associated with an improvement in individuals' overall quality of life, especially in regard to their physical function and self-esteem (Kolotkin et al., 2001; Scheen et al., 2006).

Currently, there are three main approaches to the treatment of obesity, with the initial implementation of these approaches dependent upon one's starting BMI as well as the presence of obesity-related comorbidities (Table 1). A combination of diet, physical activity and behavioral modification is recommended for individuals with a BMI 25 - 26.9 kg/m^2 with accompanying comorbidities, and for individuals with a BMI ≥27 kg/m^2 with or without comorbidities. The use of pharmacotherapy can be considered in individuals with a BMI 27 - 29.9 kg/m^2 with accompanying comorbidities, and for individuals with a BMI ≥30 kg/m^2 with or without comorbidities. Surgical interventions may be first considered for individuals with a BMI 35 - 39.9 kg/m^2 with accompanying comorbidities, and for individuals with a BMI ≥40 kg/m^2 with or without comorbidities (NHLBI Clinical Guidelines, 2000).

Table 1 Summary of Current Obesity Treatment Paradigms

Treatment Paradigm	BMI (kg/m^2)				
	25-26.9	**27-29.9**	**30-34.9**	**35-39.9**	**≥40**
Diet, physical activity, and behavioral modification	With comorbidity	✓	✓	✓	✓
Pharmacotherapy		With comorbidity	✓	✓	✓
Surgery				With comorbidity	✓

Unfortunately, the currently available obesity treatment modalities are few and have important limitations. The mainstay, diet and exercise, seldom results in sustainable weight loss, (NHLBI Clinical Guidelines, 1998) and many individuals find it hard to adhere to diet and exercise programs alone. Unlike the situation for other metabolic diseases such as

hypertension and type 2 diabetes, there are a limited number of obesity pharmacotherapies available. This is especially problematic given that the needs of the obese patient vary based on age, sex, menopausal status, comorbidities, and other factors. Although orlistat is approved for long-term use and provides efficacy beyond that usually achievable using diet and exercise alone, it is not well-tolerated by some patients. Other available pharmacotherapies, such as phentermine, and other stimulants are approved for short-term use only. While more invasive options (e.g., gastric banding, bariatric surgery) do result in greater weight loss than is achievable with pharmacotherapy, these are targeted primarily to those patients with the highest BMI. The benefit of surgical options is also offset by greater expense and risk. In the face of such limited options, patients often resort to the use of off-label medications or dietary supplements that may be ineffective or unsafe. In this context, agents such as NB may offer very viable alternatives for many obese patients, especially those who have not yet progressed to higher BMIs.

1.2 Rationale for Development

Orexigen Therapeutics Inc. has completed the Phase 3 development of a novel combination product for the treatment of obesity (proposed trade name Contrave, but hereafter referred to as NB except in specific contexts such as the proposed indication statement and dosing recommendations) composed of bupropion, a relatively weak inhibitor of the neuronal uptake of norepinephrine (NE) and dopamine (DA), combined with naltrexone, a mu-opioid receptor antagonist. Bupropion and naltrexone have been individually used in the U.S. for over 20 years for chronic indications at doses comparable to (bupropion) or greater than (naltrexone) those recommended for NB for the treatment of obesity. Since their initial approval in the U.S., there have been over 50 million unique exposures to bupropion and over 1 million unique patient exposures to naltrexone,[2] thereby resulting in a well-understood and accepted risk/benefit profile in the relevant patient populations.

Bupropion hydrochloride (HCl) was first approved in the U.S. in 1985 under the trade name Wellbutrin® for the treatment of major depressive disorder, but was voluntarily withdrawn in 1986 as a result of an increased incidence of seizures. In 1989, bupropion was re-introduced to the market with revised labeling and lower maximum dose allowed (up to 450 mg/day) to reduce the risk of seizures observed at higher doses. In 1997, bupropion was approved (under the trade name Zyban®) as an aid for use in smoking cessation, and in 2006 for the treatment of seasonal affective disorder. Currently, bupropion HCl is marketed as three formulations: an immediate-release (IR) tablet (Wellbutrin®) and a sustained-release (SR) tablet (Wellbutrin SR®) for the treatment of major depressive disorder, an extended-release (XL) tablet (Wellbutrin XL®) for the treatment of major depressive disorder and seasonal affective disorder, and as a sustained-release formulation (Zyban®) as an aid to smoking cessation treatment. Generic versions of each innovator formulation have also been approved by FDA. Bupropion hydrobromide (Aplenzin™) is an XL formulation also approved for the treatment of major depressive disorder. The current prescribing information for Wellbutrin SR® (2010) can be found in Appendix 1.

[2] Estimates Based on Wolters Kluwer Rx and Patient Data, Jan – Dec 2009 and IMS Health Rx and Persistence Data, Jan 1985 – Dec 2009.

Naltrexone IR is currently approved for the treatment of opioid addiction (approved in 1984) and alcohol dependence (approved in 1994) (under the trade names ReVia® [formerly Trexan®] and Depade®). The current prescribing information for ReVia® (2001) can be found in Appendix 1. In 2006, naltrexone was reviewed and approved in the U.S. as a long-acting injectable suspension (Vivitrol®) for the treatment of alcohol dependence, and in 2010 for the treatment of opioid dependence.

Table 2 Naltrexone and Bupropion Experience

Approval Date	Drug name/Active Ingredient	Indication and/or Dosage form	Number of Patients Exposed
Naltrexone			
Oct 2010	VIVITROL (naltrexone for extended-release injectable suspension)	Relapse to opioid dependence	~1 million
Aug 2009	EMBEDA (morphine sulfate and naltrexone HCl)	Management of moderate to severe pain	
Apr 2006	VIVITROL (naltrexone for extended-release injectable suspension)	Alcohol dependence	
Dec 1994	ReVia (Naltrexone HCl)	Alcohol dependence	
Nov 1984	ReVia (Naltrexone HCl)	Opioid addiction	
Bupropion (300-450 mg/day)[a]			
Apr 2008	APLENZIN (bupropion hydrobromide)	Major depressive disorder	~ 50 million
Jun 2006	Wellbutrin XL (bupropion HCl)	Seasonal affective disorder	
Aug 2003	Wellbutrin XL (bupropion HCl)	Extended release formulation	
May 1997	ZYBAN (bupropion HCl)	Smoking cessation	
Oct 1996	Wellbutrin SR (bupropion HCl)	Sustained release formulation	
Dec 1985	Wellbutrin (bupropion HCl)[b]	Major depressive disorder	

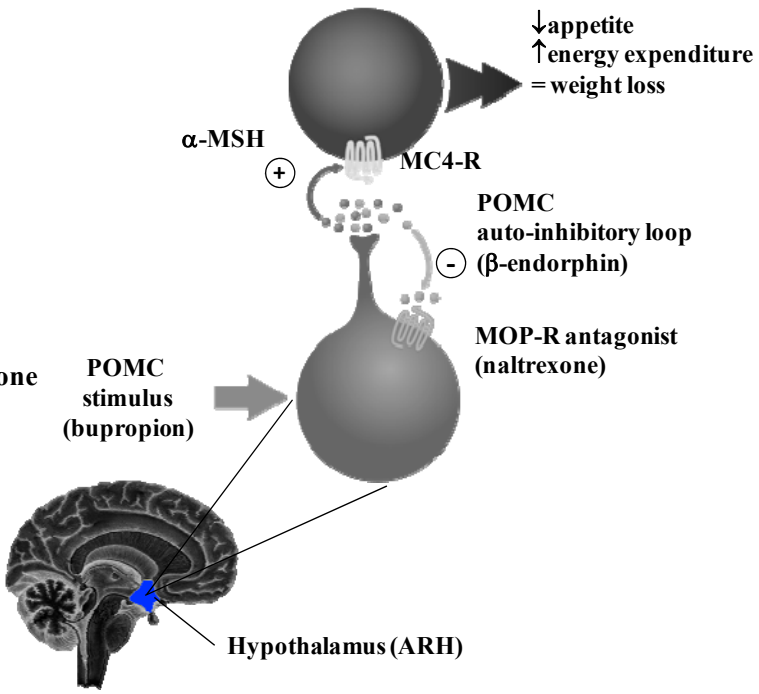
a. The maximum dose of the SR formulation is 400 mg/day and the maximum dose of the IR and XL formulations is 450 mg/day.
b. Re-introduced to the market in 1989 with revised dosing recommendations to reduce seizure risk.

Both pharmacological mechanisms addressed by NB (opioid receptor antagonism and catecholamine reuptake inhibition) have been previously explored in obesity. Opioid antagonists (including naltrexone) do not yield meaningful effects on body weight whereas bupropion has been associated with modest weight loss in clinical trials for both major depression as well as in obese patients. Bupropion has been shown to stimulate hypothalamic pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (α-MSH) which, in turn, binds to MC4 receptors (Figure 1). The binding of α-MSH to MC4 receptors initiates a cascade of actions that results in reduced energy intake and increased energy expenditure (Cowley et al., 1999). When α-MSH is

released, POMC neurons simultaneously release β-endorphin, an endogenous agonist of the mu-opioid receptor. Binding of β-endorphin to mu-opioid receptors on POMC neurons mediates a negative feedback loop on POMC neurons leading to a decrease in the release of α-MSH (Cowley et al., 2001; Ibrahim et al., 2003; Kelly et al., 1990; Loose and Kelly, 1990). Blocking this inhibitory feedback loop with naltrexone is thought to facilitate a more potent and longer-lasting activation of POMC neurons, thereby amplifying effects on energy balance. As a result, co-administration of bupropion and naltrexone produces a substantially greater effect on the POMC firing rate than either compound administered alone, suggesting that the drugs act synergistically.

Figure 1 Mechanism of Action of NB

- **POMC**
  - **Integrate multiple energy balance signals**
  - **Increased firing leads to weight loss**
  - **Activated by bupropion**
- **β-Endorphin**
  - **Released with α-MSH**
  - **Inhibits POMC firing**
  - **Effect blocked by naltrexone**



2 PROPOSED INDICATION AND DOSAGE AND ADMINISTRATION STATEMENTS

2.1 Proposed Indication

Contrave is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification.

Contrave is recommended for patients with an initial body mass index ≥30 kg/m^2 or ≥27 kg/m^2 with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension).

2.2 Proposed Dosage and Administration

The recommended daily dose of Contrave is two 8/90 tablets (i.e., 8 mg naltrexone/90 mg bupropion) 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 tablets	One CONTRAVE 8/90 tablet
Week 4 – Onward (Maintenance Dose)	Two CONTRAVE 8/90 tablets	Two CONTRAVE 8/90 tablets

As noted above, 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. The tablets should not be cut, chewed, or crushed. Doses above 32/360 mg/day (4 tablets daily) are not recommended.

Treatment initiation and escalation with Contrave 4/90 tablets (i.e., 4 mg naltrexone/90 mg bupropion) may also be considered. If well tolerated, patients using Contrave 4/90 tablets should switch to Contrave 8/90 tablets to have their daily dose increased to the recommended maintenance daily dose of 32 mg naltrexone and 360 mg bupropion (two Contrave 8/90 tablets twice daily) to maximize weight loss. Conversely, patients initiated with Contrave 8/90 tablets that experience treatment intolerance during the escalation or early maintenance period can be switched to Contrave 4/90 tablets, resulting in a daily maintenance dose of 16 mg naltrexone and 360 mg bupropion (Table 3).

Table 3 NB Doses and Regimen Proposed for Marketing

Tablet Strength	Dosing Regimen	Total Daily Maintenance Dose
4 mg naltrexone SR/90 mg bupropion SR	2 tablets twice daily (BID)	16 mg naltrexone SR/360 mg bupropion SR (NB16)
8 mg naltrexone SR/90 mg bupropion SR	2 tablets twice daily (BID)	32 mg naltrexone SR/360 mg bupropion SR (NB32)

Most patients who respond to Contrave will have done so by 4 months of treatment. If a patient has not exhibited clinically meaningful weight loss (e.g., at least 5%) after 4 months of treatment, the physician should consider discontinuation of Contrave and initiation of other weight management strategies.

Patients may experience elevated blood pressure or pulse during Contrave treatment; the risk may be greater during the initial 3 months of therapy. If clinically relevant and sustained (e.g., at least two consecutive measurements) increases in blood pressure or pulse occur, Contrave should be discontinued. As patients with hypertension or a history of hypertension may be at increased risk of blood pressure elevations, care should be exercised when initiating treatment with Contrave in such patients.

3 NONCLINICAL

Since New Drug Application (NDA) 200063 was submitted as a 505(b)(2) application, reference is made to the previous findings of the FDA regarding the safety and efficacy of ReVia® and Wellbutrin SR®. Given the existing nonclinical safety studies of the individual components (described in Appendix 2) showed no potential for overlapping toxicity and prior clinical experience with the combination revealed no new effects, it was concluded that additional studies in animals were not warranted. A hERG (human ether-a-go-go related gene) evaluation was conducted for naltrexone and its primary metabolite 6β−naltrexol to provide additional safety pharmacology information. No appreciable inhibition of hERG was observed in this study.

The molecular pharmacology of naltrexone and bupropion is well described in the literature and summarized in the respective labels as are the results of nonclinical studies specific to their approved indications. Results of nonclinical studies investigating mechanism of action and efficacy for the proposed indication of obesity are described in the following section.

3.1 Mechanism of Action for the Combination

The mechanism of action of the proposed naltrexone/bupropion combination therapy for the treatment of obesity is based on basic research on the biology of appetite and metabolism regulation, nonclinical and clinical data with the proposed drugs administered individually and in combination, and the pharmacology of the hypothalamic regulation of food intake.

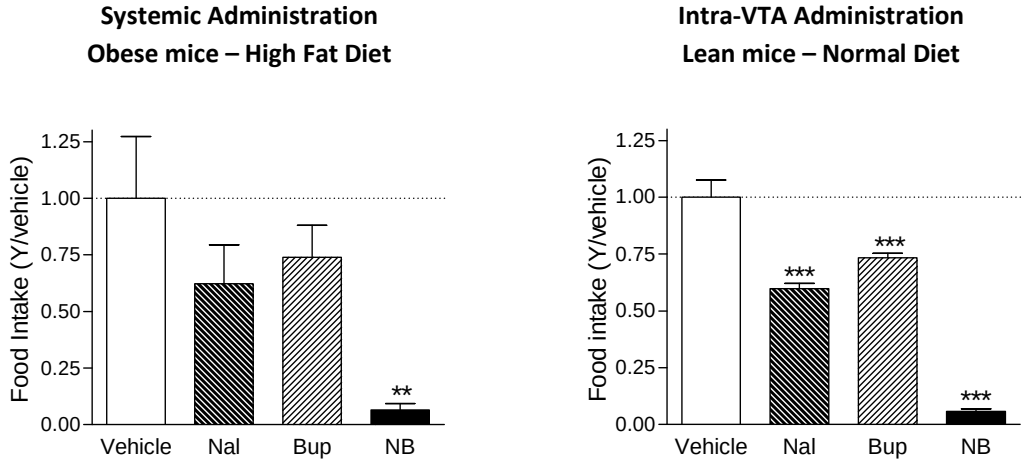
Key circuitry controlling food intake and energy expenditure resides in the arcuate nucleus of the hypothalamus. POMC neurons release alpha-melanocortin stimulating hormone (α-MSH), which binds to MC4 receptors and initiates a cascade of actions that results in reduced energy intake and increased energy expenditure (Cowley et al., 1999). When α-MSH is released, POMC neurons simultaneously release β-endorphin, an endogenous agonist of the mu opioid receptor (Figure 1). Binding of β-endorphin to mu opioid receptors on POMC neurons mediates a negative feedback loop on POMC neurons leading to a decrease in the release of α-MSH (Cowley et al., 2001; Ibrahim et al., 2003; Kelly et al., 1990; Loose and Kelly, 1990).

Blocking this inhibitory feedback loop with naltrexone is proposed to facilitate a more potent and longer-lasting activation of POMC neurons, thereby amplifying the effects of bupropion on energy balance. Bupropion increases the firing rate of POMC neurons as shown in hypothalamic slices from POMC-enhanced green fluorescent protein mice, while naltrexone has minimal effect (Greenway et al., 2009). Co-administration of bupropion and naltrexone produces a substantially greater effect on firing rate than either compound administered alone, suggesting that the drugs act synergistically.

These putatively synergistic effects of naltrexone and bupropion at the cellular level are supported by *in vivo* studies of feeding behavior. Both bupropion (1.5-90 mg/kg, IP) and naltrexone (1.5-30 mg/kg, IP) dose-dependently decrease food intake in lean (normal weight) and obese mice (Greenway et al., 2009). When doses of bupropion (20 mg/kg) and naltrexone (1 mg/kg) with moderate individual effects on food intake were then co-administered, a greater effect on food intake was observed.

The mesolimbic reward pathway, which mediates many goal-directed behaviors (Koob and Nestler 1997; Nestler 2005), represents a second mechanism through which bupropion and naltrexone may act together on feeding behavior. Dopamine and endogenous opioid peptides are key neurotransmitters influencing the activity of this pathway (Koob and Nestler 1997). In particular, the ventral tegmental area (VTA) is an important structure in the mesolimbic system, as it contains dopaminergic cell bodies that project to the nucleus accumbens, a brain area involved in mediating reward. Administration of bupropion and naltrexone, in combination, directly into the VTA in lean mice produced significantly greater decreases in short-term food intake than either drug when administered alone (Figure 2).

Figure 2 Effect of Naltrexone and Bupropion Administration Alone and in Combination on Food Intake



** p<0.01 and *** p<0.001 vs. vehicle. Data are mean + SE.
Systemic administration data based on Greenway et al., 2009. Intra-VTA administration based on Sinnayah et al., 2007.
Abbreviations: Bup=bupropion; Nal=naltrexone; NB=Nal+Bup combination dosing; SE=standard error; VTA=ventral tegmental area.

4 OVERVIEW OF THE NB CLINICAL DEVELOPMENT PROGRAM

The NB clinical development program was designed and conducted in accordance with the current FDA draft guidance (Guidance for Industry: Developing Products for Weight Management; February 2007) as well as taking into account feedback provided by the Division of Metabolism and Endocrinology Products (DMEP) throughout the program. As detailed below, the development program fulfilled requirements set forth in the aforementioned FDA guidances, including:

- adequate patient exposure;
- enrollment of the appropriate patient population (i.e., obese and overweight patients with comorbidities, including type 2 diabetes);
- demonstration of the contribution of the individual components to efficacy;
- use of a co-primary endpoint in the pivotal studies based on mean and categorical changes in body weight; and
- demonstration of efficacy in trials for at least one-year in length.

Orexigen's clinical development program (Appendix 3) is composed of 23 completed trials, including 15 Phase 1, four Phase 2, and four pivotal Phase 3 studies. These 23 studies allowed for a thorough assessment of the safety, efficacy and pharmacokinetics (PK) of NB.

Across the Phase 2 and Phase 3 studies, a total of 3475 patients have been exposed to NB for a total of 2313 patient-years, including:

- 635 patients who received NB16 (16 mg naltrexone + either 360 or 400 mg bupropion SR);
- 2695 who received NB32 (32 mg naltrexone + either 360 or 400 mg bupropion SR); and
- 269 who received at least one dose of NB48/50 (includes both NB48 [48 mg naltrexone + either 360 or 400 mg bupropion SR] and NB50 [50 mg naltrexone + 300 mg bupropion SR]). Patients in Study NB-303 who were re-randomized from NB32 to NB48 are included in this summary using their duration of exposure on the NB48 dose and also under the NB32 summary using their duration of exposure on NB32.

Of the 3475 patients, nearly one-half (1661 patients; 47.8%) received NB for at least one year.

The 15 Phase 1 studies were conducted as part of the formulation development and clinical pharmacology programs. A number of these studies utilized crossover designs which accommodated multiple objectives (e.g., establishing both the effect of food on the PK of NB as well as investigating potential drug-drug interactions [DDIs]). The Phase 1 program consisted of the following:

- Five comparative bioavailability/bioequivalence (BA/BE) studies (NB-221, NB-225, NB-228, NB-229, and NB-230).

- Four studies that contributed to the evaluation of the effect of food on the PK of NB (NB-233, NB-236, NB-237, and NB-239).
- Four trials that assessed the potential of PK DDIs between NB tablets and representative medications from pharmacological classes likely to be prescribed in parallel with NB (NB-232, NB-233, NB-234, and NB-236).
- Four studies that examined the PK of a new formulation of NB (combination monolayer tablets) that is not currently under review (NB-231, NB-237, NB-238 and NB-239).

The Phase 2 program consisted of four completed studies, as summarized below:

- Two studies (OT-101 [24-week proof of concept] and NB-201 [24-weeks of double-blind treatment with a 24-week extension]) were conducted to examine the weight loss efficacy, safety and tolerability of the combination of naltrexone and bupropion compared with the individual components and placebo in obese patients. The results of these two studies helped determine the study designs and doses of NB evaluated in Phase 3.
- Two open-label studies were completed in special populations of overweight and obese patients (i.e., nicotine-dependent patients [NB-401] and patients who had major depression [NB-402]).

The NB Phase 3 program included four pivotal, 56-week, multicenter, randomized, double-blind, placebo-controlled studies (Studies NB-301, NB-302, NB-303, and NB-304) in obese and overweight patients. Across these studies the efficacy, safety and tolerability of NB were evaluated in three settings:

- In patients who received customary diet and behavioral counseling, including prescribed exercise (Studies NB-301 and NB-303).
- In patients who underwent intensive lifestyle modification counseling (Study NB-302).
- In patients who had type 2 diabetes (Study NB-304) and who received customary diet and behavioral counseling.

Consistent with the FDA guidance on weight management products, Studies NB-301, NB-302 and NB-303 enrolled patients with a BMI $\geq$30 and $\leq$45 kg/m^2 for patients with uncomplicated obesity, or with a BMI $\geq$27 and $\leq$45 kg/m^2 for obese or overweight patients with controlled hypertension and/or dyslipidemia. Also, as recommended by the FDA guidance, one study (Study NB-304) was conducted in obese and overweight patients with type 2 diabetes.

In each of the four Phase 3 studies, the efficacy of NB was established using the FDA-recommended co-primary endpoints of mean change from baseline in body weight and the proportion of individuals who achieved a $\geq$5% reduction in body weight from baseline following 1 year of treatment.

5 CLINICAL PHARMACOLOGY

NB is composed of two drugs (bupropion and naltrexone) whose clinical pharmacology is well characterized in the literature and U.S. Prescribing Information of approved products. Orexigen-sponsored studies (Appendix 3) furthered this understanding by collecting data on the following:

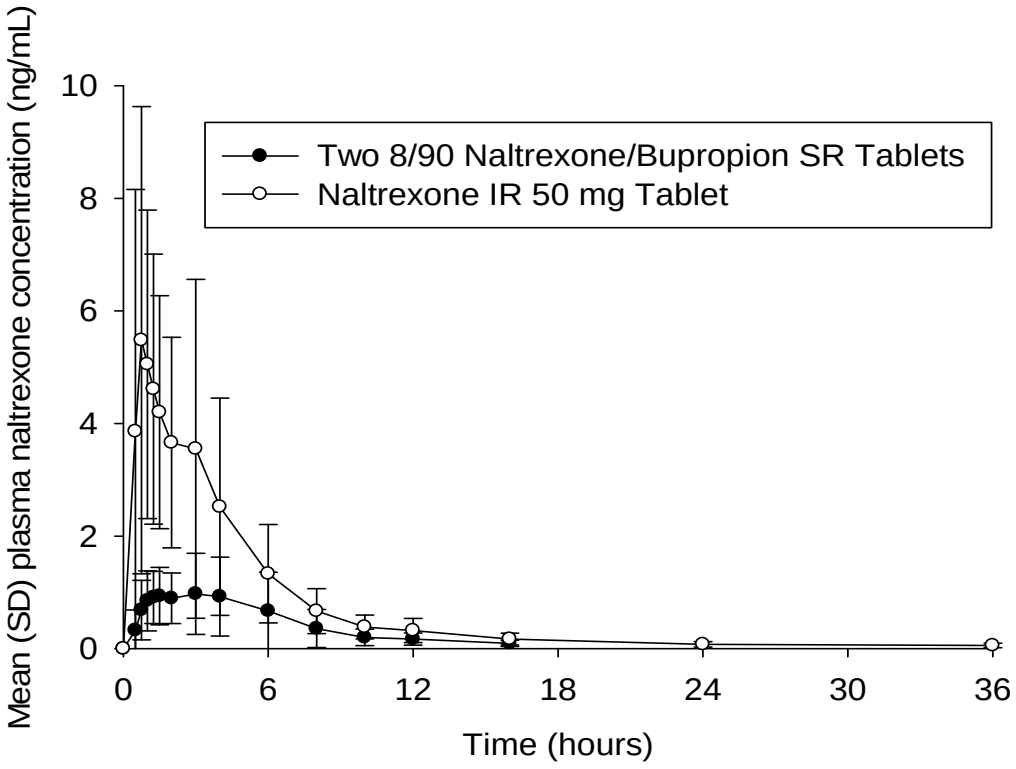
- Naltrexone and bupropion PK from NB relative to the individual agents
- Naltrexone receptor occupancy data to guide dose selection
- In vitro metabolism and Organic Cation Transporter (OCT2) transporter studies
- Clinical DDI studies with relevant concomitant medications
- PK of NB in the intended obese population
- Population PK and exposure-response analyses

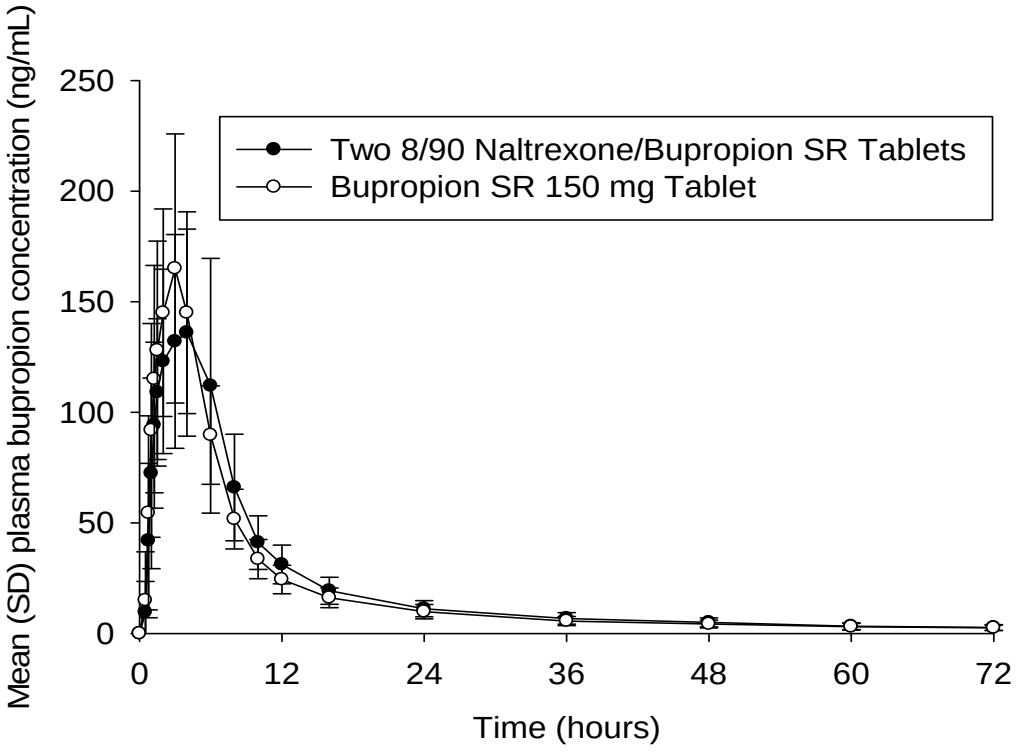
5.1 Pharmacokinetics

5.1.1 Absorption and Distribution

NB extended-release tablets have bioequivalent extent of exposure (area under the curve [AUC]) on a mg-to-mg basis compared to naltrexone immediate-release (IR) or bupropion sustained-release (SR) tablets administered as single agents. Peak concentrations of naltrexone and bupropion occurred approximately 2 and 3 hours post-administration of NB, respectively (Figure 3). There were no meaningful differences in the bioavailability or elimination of naltrexone or bupropion when administered in combination compared to each administered alone. Due to the extended nature of the drug release for NB, the maximum plasma concentration (C_{max}) for naltrexone was markedly reduced (5.6-fold) on a mg-to-mg basis compared to 50 mg naltrexone IR administered alone. The bupropion C_{max} from NB (180 mg) was equivalent to the C_{max} of bupropion SR 150 mg.

Figure 3 Naltrexone and Bupropion Pharmacokinetics from NB and Approved Products





Abbreviations: IR= Immediate Release; SR= Sustained release.
Results obtained in Study NB-230; N=27.

Naltrexone and bupropion are well absorbed, although naltrexone has low bioavailability due to extensive first pass metabolism.

Plasma protein binding is not extensive for naltrexone (21%) or bupropion (84%), indicating low potential for drug interactions by displacement.

PK exposure increased with food (at steady state, food effect increased AUC and C_{max} by 70% and 92% for naltrexone, and 12% and 28% for bupropion, respectively). These differences with food are unlikely to be clinically meaningful, as exposures remain at or below those of currently approved bupropion- and naltrexone-containing products.

5.1.2 Metabolism and Excretion

Following single oral administration of NB tablets to healthy patients, the mean elimination half-life was approximately 5 hours for naltrexone. The major metabolite of naltrexone is 6-beta-naltrexol, which is less potent than naltrexone, but eliminated more slowly and circulates at much higher concentrations than naltrexone. Naltrexone and 6-beta-naltrexol are not metabolized by cytochrome P450 (CYP) enzymes and have no known potential for inhibition or induction of P450 isozymes.

The bupropion mean elimination half-life was 21 hours. Bupropion is extensively metabolized with three active metabolites: hydroxybupropion, threohydrobupropion and erythrohydrobupropion by both oxidative and non-oxidative pathways. The metabolites have longer elimination half-lives than bupropion and accumulate to a greater extent, thereby making important contributions to efficacy at steady-state. Following twice daily administration of NB, steady-state concentrations are achieved in approximately one week (as determined by the longest lived metabolite of bupropion).

Naltrexone, bupropion and their metabolites are excreted primarily by the kidney with very little urinary excretion of parent drugs.

5.2 Special Populations

5.2.1 Sex, Race, Body Size (e.g., BMI), and Smoking Status

Pooled analyses of NB data across single- and multiple-dose studies revealed no meaningful differences in the pharmacokinetic parameters of naltrexone, bupropion or their metabolites based on sex, race, body size or baseline smoking status; therefore, no dosage adjustment is necessary based on these factors.

5.2.2 Elderly

The pharmacokinetics of NB have not been evaluated in the geriatric population, and the effects of age on the pharmacokinetics of naltrexone or bupropion and their metabolites have not been fully characterized. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

5.2.3 Renal or Hepatic Impairment

The pharmacokinetics of NB have not been evaluated in patients with renal or hepatic impairment. Based on information available for the individual constituents, NB should be used with caution in patients with moderate and severe renal impairment since the metabolites for both components are cleared primarily through the kidneys. In addition, it is known that hepatically-impaired patients have reduced clearance of the components of NB and, therefore, NB should not be used in patients with severe hepatic disease.

5.3 Drug Interactions

Appendix 4 describes assessments of the drug-drug interaction potential of NB based on Orexigen-sponsored studies or published information on the individual constituents. Key findings are as follows:

- In vitro studies have confirmed that naltrexone does not have the potential to inhibit or induce cytochrome P450 (CYP) enzymes and has no known PK drug-drug interactions (aside from changes attributed to the effect of food).
- While bupropion is commonly used in combination with selective serotonin reuptake inhibitor (SSRI) antidepressants, co-administration of NB with drugs that are metabolized by the CYP2D6 isozyme should be approached with caution as bupropion can increase the PK concentrations of CYP2D6 substrates by noncompetitive inhibition.
- Co-administration of drugs that induce the metabolism of bupropion and its metabolites (e.g., carbamazepine, lopinavir, rifampin) may lead to potentially reduced efficacy of NB.
- Metabolic inhibition of CYP2B6 is unlikely to result in clinically meaningful effects on bupropion due to the multiple metabolic pathways of bupropion.
- Bupropion and its active metabolites inhibit in vitro metformin uptake in cells expressing human OCT2. NB co-administration could result in increased exposure of metformin or other OCT2 substrates (e.g., pindolol, ranitidine and varenicline) in a manner similar to cimetidine.

5.4 Exposure-Response Assessments

Exposure-response (PK/PD) assessments were performed using noncompartmental or univariate correlation and multivariate (population-based) methodologies. These studies conducted primarily following single doses of two 8/90 tablets or at steady-state following two 8/90 tablets BID (NB32) did not identify specific relationships between NB PK exposure and selected safety and efficacy measures. Treatment effects on weight loss and secondary efficacy endpoints were seen across a wide range of naltrexone and bupropion exposures. Similarly, nausea, slight elevations in creatinine and blood pressure, and other treatment-related changes were not related to exposure. There was no correlation observed between plasma concentrations and vital sign changes from baseline in Phase 1 studies. In addition, no relationship between therapeutic plasma concentrations of bupropion, naltrexone, or their active metabolites and duration of the QT or corrected QT interval was observed in single-dose Phase 1 studies or after 4 and 56 weeks of treatment in Study NB-303.

6 EFFICACY

6.1 Introduction

The efficacy of NB has been established by the results of Phase 2 Study NB-201 as well as the four pivotal Phase 3 studies (NB-301, NB-302, NB-303 and NB-304). NB dose selection for the Phase 2 clinical trials was determined based on the approved doses of the individual components, the scientific literature on bupropion and naltrexone, and results from a positron emission tomography (PET) study that evaluated opiate receptor occupancy with naltrexone doses between 16 and 48 mg/day. NB efficacy, safety and tolerability results from the Phase 2 studies helped determine the study designs and doses of NB evaluated in Phase 3 (Sections 6.2, 6.3, and 6.4, respectively).

A summary of the key details of the Phase 2 and 3 studies is provided in Table 4.

Table 4 Summary of Clinical Studies Establishing the Efficacy of NB

Study ID	Phase	Study Design	Test Product and Dose	No. of Patients Randomized	Treatment Duration	Age, Sex[a]	Study Population	Primary Endpoint(s)
OT-101	2	Multicenter, randomized, single-blind placebo- and monotherapy study	Placebo[b] Naltrexone 50 mg/day[b] (Nal50) Bupropion SR 300 mg/day (B300) Naltrexone 50 mg/day and Bupropion SR 300 mg/day (Nal50/B300)	Placebo: 59 Nal50: 60 B300: 59 Nal50/B300: 60 Crossover:Placebo to Nal50/B300: 18 Nal50 to Nal50/B300: 16	16-week primary treatment period followed by an optional 32-week extension period[c]	18 to 60 years, male (11%) and female (89%)	Obese patients without complicated obesity who are nonsmokers	Percent and absolute change from baseline to endpoint in body weight
NB-201	2	Multicenter, randomized, double-blind, placebo- and monotherapy - controlled study	Placebo[b] Naltrexone 48 mg/day[b] (Nal48) Bupropion SR 400 mg/day (B400) Naltrexone 16 mg/day and Bupropion SR 400 mg/day (Nal16/B400) Naltrexone 32 mg/day and Bupropion SR 400 mg/day (Nal32/B400) Naltrexone 48 mg/day and Bupropion SR 400 mg/day (Nal48/B400)	Placebo: 88 Nal48: 61 B400: 66 Nal16/B400: 67 Nal32/B400: 70 Nal48/B400: 67 Crossover: Placebo to Nal32/B400: 61 Nal48 to Nal32/B400: 34	24-week double-blind, followed by 24-week extension	18 to 60 years, male (12%) and female (88%)	Obese patients without complicated obesity who are nonsmokers with a BMI $\geq$30 and $\leq$40 kg/m^2	Percent change from baseline to endpoint in body weight

Table 4 Summary of Clinical Studies Establishing the Efficacy of NB (*Continued*)

Study ID	Phase	Study Design	Test Product and Dose	No. of Patients Randomized	Treatment Duration	Age, Sex[a]	Study Population	Primary Endpoint(s)
NB-301	3	Multicenter, randomized, double-blind, placebo-controlled study	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)	Placebo: 581 NB16: 578 NB32: 583 For the NB-301 Substudy DEXA Placebo: 77 NB16 and 32: 137	56-week double-blind (and a 2-week double-blind discontinuation assessment during Weeks 57-58)	18 to 66 years, male (15%) and female (85%)	Obese patients with uncomplicated obesity (no presence of hypertension, dyslipidemia, or type 2 diabetes) with a BMI ≥30 and ≤45 kg/m^2 and; Obese and overweight patients with controlled hypertension and/or dyslipidemia with a BMI ≥27 and ≤45 kg/m^2	Percent change from baseline to endpoint in body weight Proportion of patients with ≥5% weight loss from baseline For the NB-301 Substudy Change from baseline in total fat mass
NB-302	3	Multicenter, randomized, double-blind, placebo-controlled study that included intensive lifestyle modification counseling	Placebo Naltrexone SR 32 mg/day and Bupropion SR 360 mg/day (NB32)	Placebo: 202 NB32: 591	56-week double-blind	19 to 65 years, male (10%) and female (90%)	Obese patients with uncomplicated obesity (no presence of hypertension, dyslipidemia, or type 2 diabetes) with a BMI ≥30 and ≤45 kg/m^2 and; Obese and overweight patients with controlled hypertension and/or dyslipidemia with a BMI ≥27 and ≤45 kg/m^2	Percent change from baseline to endpoint in body weight Proportion of patients with ≥5% weight loss from baseline

Table 4 Summary of Clinical Studies Establishing the Efficacy of NB (*Continued*)

Study ID	Phase	Study Design	Test Product and Dose	No. of Patients Randomized	Treatment Duration	Age, Sex[a]	Study Population	Primary Endpoint(s)
NB-303	3	Multicenter, randomized, double-blind, placebo-controlled study	Placebo Naltrexone SR 32 mg/day and Bupropion SR 360 mg/day (NB32) From Week 28 through Week 44, non-responders on NB32 were re-randomized to either continue on NB32 or change to Naltrexone SR 48 mg/day and Bupropion SR 360 mg/day (NB48)	Placebo: 495 NB32: 1001 Re-randomized to NB48: 123 <u>For the NB-303 Substudy ABPM</u> Placebo: 59 NB32: 121	56-week double-blind	18 to 65 years, male (15%) and female (85%)	Obese patients with uncomplicated obesity (no presence of hypertension, dyslipidemia, or type 2 diabetes) with a BMI ≥30 and ≤45 kg/m^2 and; Obese and overweight patients with controlled hypertension and/or dyslipidemia with a BMI ≥27 and ≤45 kg/m^2	Percent change from baseline to endpoint in body weight Proportion of patients with ≥5% weight loss from baseline Primary efficacy evaluation was conducted at Week 28 with secondary evaluation at Week 56 <u>For the NB-303 Substudy</u> Evaluation of the change from baseline in average 24-hour systolic and diastolic blood pressure
NB-304	3	Multicenter, randomized, double-blind, placebo-controlled study	Placebo Naltrexone SR 32 mg/day and Bupropion SR 360 mg/day (NB32)	Placebo: 170 NB32: 335	56-week double-blind	20 to72 years, male (44%) and female (56%)	Obese and overweight patients with type 2 diabetes mellitus and with or without controlled hypertension and/or dyslipidemia with a BMI ≥27 and ≤45 kg/m^2	Percent change from baseline to endpoint in body weight Proportion of patients with ≥5% weight loss from baseline

Abbreviations: NB=all doses of combination naltrexone and bupropion treatment, Nal=naltrexone, B=bupropion SR.

a. The age ranges and percentages of males and females presented in this table reflect the actual population enrolled in each study.

b. The patients in these treatment groups crossed over to treatment with both drugs during the extension phase.

c. Study OT-101 was stopped early (through Week 24) due to lack of statistically significant differences in the primary efficacy endpoint at Week 16 between bupropion and NB.

6.2 Study OT-101

Study OT-101 was a randomized, naltrexone-blind, placebo-controlled, proof-of-concept study that investigated the safety and efficacy of daily doses of the combination of commercially-available naltrexone IR 50 mg (administered as a single dose of 50 mg) and bupropion SR 300 mg (administered as two divided daily doses of 150 mg each) vs. bupropion SR monotherapy (300 mg/day), naltrexone monotherapy (50 mg/day), and placebo.

Forty-seven percent of NB patients were 24-week completers compared to 53% for bupropion monotherapy. Results from this study demonstrated the NB combination resulted in a statistically significant reduction from baseline in body weight compared with placebo and naltrexone monotherapy at Week 16 in the intent-to-treat (ITT) analysis set. The differences between NB and bupropion were not statistically significant at Week 16 and, as a result, the study was terminated early (prior to the originally planned Week 48 endpoint). However, at the Week 24 endpoint, there was numerically greater efficacy in NB- compared with bupropion-treated patients (p=0.06) in the completer subgroup. Nausea was the most common adverse event (AE) with NB (31%), compared with 35% with naltrexone, and 9% for bupropion. The results of this study influenced the subsequent NB clinical development program, as described below.

6.3 Study NB-201

Study NB-201 was a double-blind, placebo- and monotherapy-controlled study in which the safety and efficacy of three total daily doses of NB (administered as a combination of commercially-available bupropion SR and investigational naltrexone IR formulations) were investigated versus the individual active components and placebo in obese patients.

The primary efficacy objective was to evaluate the percent change from baseline in total body weight of three combinations of naltrexone with bupropion, compared to the control groups, over 24 weeks of treatment. Treatments of bupropion alone or in combination with naltrexone were further evaluated for an additional 24 weeks. The longer duration of NB-201 was expected to allow better characterization of the pattern of weight loss observed across the bupropion monotherapy and NB groups.

6.3.1 Dose Selection for NB-201

The limited efficacy of the NB combination observed in Study OT-101 led to several changes in Study NB-201. The dose of bupropion was increased to 400 mg/day (administered as two divided daily doses of 200 mg) based on published data demonstrating a dose-response for bupropion and weight loss (Anderson et al., 2002; Settle et al., 1999). This dose increase was expected to lead to increased efficacy. Three doses of naltrexone were tested (16, 32 and 48 mg/day) based on the results of an Orexigen-sponsored human opiate receptor occupancy study using positron emission tomography (PET). This study demonstrated adequate receptor occupancy (>60%) with naltrexone doses as low as 8 mg twice daily. The combination of bupropion with lower naltrexone doses was hypothesized to lead to lower gastrointestinal events and decreased discontinuation rates.

Doses of bupropion and naltrexone were escalated in Study NB-201 as follows:

Table 5 Bupropion and Naltrexone Dosing in Study NB-201

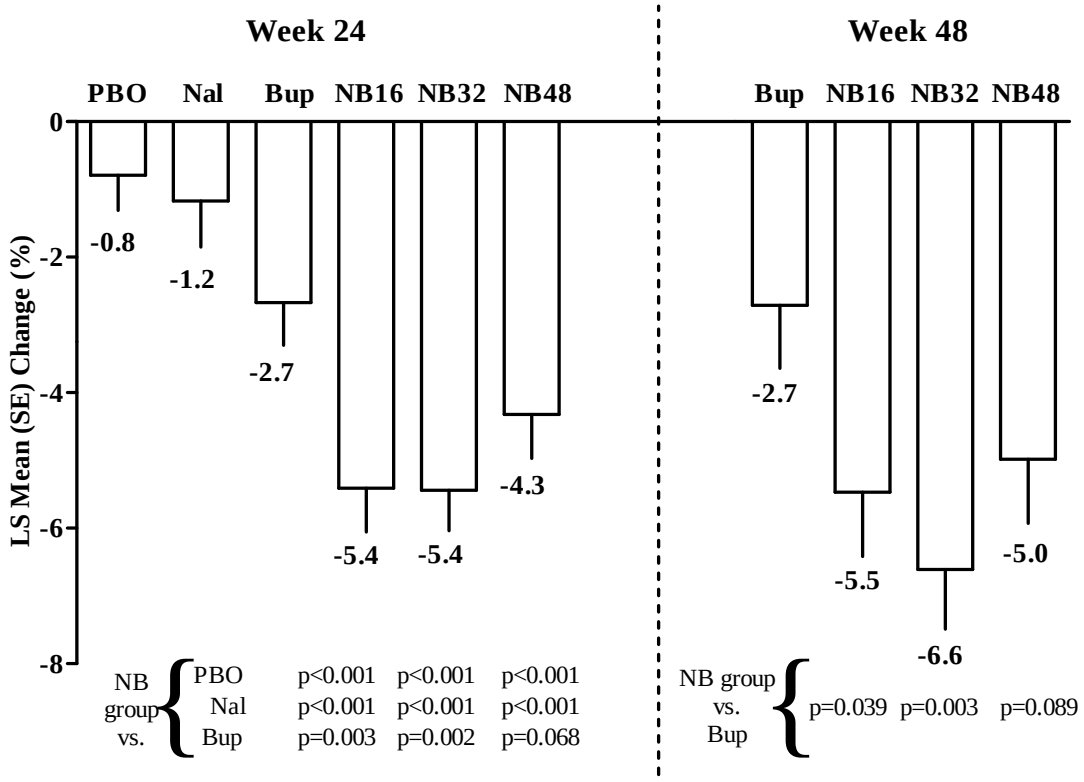
		Bupropion	Naltrexone		
Randomization Group		All patients	16 mg	32mg	48mg
Titration Phase	Days 1-3	100 mg/day	4 mg/day	8 mg/day	12 mg/day
	Days 4-7	200 mg/day	8 mg/day	16 mg/day	24 mg/day
	Weeks 2, 3, and 4	300 mg/day	12 mg/day	24 mg/day	36 mg/day
Maintenance Phase	Weeks 5-24	400 mg/day	16 mg/day	32 mg/day	48 mg/day

6.3.2 Study Results

The results of Study NB-201 demonstrated that NB16 and NB32 (Figure 4) were statistically significantly more efficacious than placebo and the individual components at the primary efficacy endpoint (Week 24). With regard to tolerability, within the NB groups, nausea and vomiting rates decreased with lower naltrexone doses. The NB48 group had the lowest completer rates at week 24 (37%), compared to 55% and 64% for NB16 and NB32 respectively.

At Week 48 (Figure 4), numerically greater efficacy was observed with NB32 (LS mean percent weight loss from baseline of -6.6%) compared with NB16 (-5.5%) in the ITT analysis; NB48 resulted in numerically greater efficacy in the completer subset (-10.7%) compared with NB32 (-8.8%) and NB16 (-8.0%).

Figure 4 Body Weight, Percent Change from Baseline to Week 24 and Week 48 in Study NB-201 (ITT-LOCF)



LS mean change from baseline for each treatment group is unadjusted for baseline factors
Abbreviations: LS mean=least squares mean; Nal=naltrexone 48 mg; Bup=bupropion SR 400 mg; NB16=naltrexone 16 mg/bupropion SR 400 mg; NB32=naltrexone 32 mg/bupropion SR 400 mg; NB48=naltrexone 48 mg/bupropion SR 400 mg; PBO=placebo; SE=standard error.

6.4 Dose Selection for Phase 3

Based on the results from Study NB-201 (Section 6.3), a bupropion SR dose of 360 mg/day was selected for Phase 3. This dose was expected to provide adequate efficacy while providing an exposure margin to the maximum bupropion SR labeled dose of 400 mg/day.

With regard to naltrexone, doses of 16, 32 and 48 mg/day were investigated in Phase 2 and Phase 3, as summarized below:

- Study NB-201 indicated a naltrexone dose of 32 mg/day, when combined with bupropion, was associated with the numerically greatest efficacy in the ITT-LOCF analysis at Week 48 and with safety and tolerability comparable to NB16. As a result, NB32 (naltrexone 32 mg/day+bupropion 360 mg/day) was chosen as the primary dose for Phase 3 and was evaluated in all four pivotal studies.
- Study NB-201 demonstrated the naltrexone 16 mg/bupropion SR 400 mg combination to also be efficacious with somewhat lower nausea rates compared with NB32. Therefore, the lower dose of NB16 (naltrexone 16 mg/day+bupropion 360 mg/day) was also evaluated in one of the pivotal Phase 3 studies (NB-301).

- Because the NB48 dose appeared less well tolerated than NB16 or NB32, this dose was not used as an initial treatment in Phase 3. Rather, in Study NB-303, NB48 (naltrexone 48 mg/day+bupropion 360 mg/day) was evaluated in patients who failed to lose at least 5% of their baseline body weight by Week 28, or who failed to maintain at least 5% weight loss compared to baseline during Weeks 32 to 44 while on NB32. The rationale for including NB48 in Phase 3 was based on its numerically greater efficacy in the Week 48 completer analysis in Study NB-201.

The doses of NB selected for Phase 3 were escalated over 3 weeks for most patients (a 4-week dose escalation was evaluated for half of the patients in Study NB-303). The use of a dose escalation regimen was based on the labeling recommendations for approved bupropion-containing products as well as the results from Studies OT-101 and NB-201, from which it was concluded that gradual increases of the dose of NB would yield lower nausea rates and improved tolerability during the Phase 3 studies.

6.5 Phase 3 Study Designs

The NB Phase 3 program included four pivotal, 56-week, multicenter, randomized, double-blind, placebo-controlled studies (Studies NB-301, NB-302, NB-303, and NB-304) in obese and overweight patients. A summary of the key study design features of the four pivotal studies are presented in Table 4, and a summary of the key inclusion/exclusion criteria shared by the four studies are described below:

Key Inclusion Criteria

- BMI Criterion
  - For Studies NB-301, NB-302, and NB-303: BMI ≥30 and ≤45 kg/m^2 for patients with uncomplicated obesity, or BMI ≥27 and ≤45 kg/m^2 for obese or overweight patients with controlled hypertension and/or dyslipidemia.
  - For Study NB-304: BMI ≥27 and ≤45 kg/m^2 for patients with type 2 diabetes mellitus with or without controlled hypertension and/or dyslipidemia
- 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
- Alanine aminotransferase (ALT) and aspartate aminotransferase (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 Self-Reported (IDS-SR) scores <2 on items 5 (sadness), 6 (irritability), 7 (anxiety/tension) and 18 (suicidality), and IDS-SR total score <30

Key Exclusion Criteria

- 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)
- 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 specific 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
- 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 $\geq$5 minutes loss of consciousness, concussion symptoms lasting $\geq$15 minutes, brain surgery, skull fracture, subdural hematoma, or febrile seizures)
- Participation in a weight loss management program within one month prior to randomization

In Studies NB-301, NB-303 and NB-304 the following concomitant medications were excluded:

- 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
- Depo-Provera®
- smoking cessation agents
- use of opioid or opioid-like medications, including analgesics
- antitussives

In Studies NB-301 and NB-303, the following concomitant medications were also excluded:

- Antidiabetic agents

In Study NB-302, the following concomitant medications were excluded:

- Antidiabetic agents
- 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 anorectic or weight loss agents
- any over-the counter dietary supplements with psychoactive, appetite or weight effects
- alpha-adrenergic blockers
- beta blockers
- clonidine
- coumadin
- theophylline
- cimetidine
- oral corticosteroids
- topiramate
- Depo-Provera®
- smoking cessation agents
- regular use of opioid or opioid-like analgesics

Within the four pivotal studies the efficacy, the safety and tolerability of NB following up to 56 weeks of treatment were evaluated in three settings:

- In patients who received customary diet and behavioral counseling, including prescribed exercise (Studies NB-301 and NB-303)

- In patients who underwent intensive lifestyle modification counseling (Study NB-302)
- In patients who had type 2 diabetes and who received customary diet and behavioral counseling (Study NB-304)

Study NB-301 included a substudy in which patients underwent a body composition analysis and visceral fat measurement at baseline and after approximately 52 weeks of therapy (Section 6.9.1.1.1). Study NB-303 included a substudy where blood pressure was measured over a 24-hour period at baseline, and after approximately 24 and 52 weeks of therapy (Section 7.6.1.1.2). PK data obtained from a subset of patients from Study NB-303 were used for population PK analyses (Section 5.4).

The program of customary diet and behavioral counseling in Studies NB-301, NB-303 and NB-304 was provided at baseline, Weeks 12, 24, 36 and 48. This program included dietary instruction (with the goal of patients achieving a 500 kcal/day deficit), behavioral modification advice, and exercise counseling. The intensive lifestyle modification counseling in Study 302 was provided weekly during the first 16 weeks of the study, then biweekly until Week 28, and then monthly thereafter. The program included dietary instruction (with the goal of patients adhering to a 1200 – 2000 kcal/day low-fat diet), prescribed exercise, and a behavioral weight loss program provided in group sessions.

Although Studies NB-301, NB-302 and NB-303 enrolled a similar patient population (i.e., obese patients with uncomplicated obesity, or obese/overweight patients with controlled hypertension and/or dyslipidemia), there were unique design elements associated with each of these studies.

- Study NB-301 investigated two daily doses of NB (NB16 and NB32). This study also evaluated the safety of abrupt or tapered NB discontinuation after 56 weeks of treatment.
- Study NB-302 assessed the efficacy and safety of NB32 in a population of obese/overweight patients undergoing an intensive behavioral modification program that included regular group counseling sessions, maintenance of food diaries, diet and exercise.
- In Study NB-303, patients who did not experience or maintain at least 5% weight loss from baseline between Weeks 28-44 while on NB32 therapy were re-randomized to continue on NB32 or increase their daily dose to NB48 to determine if the dose increase resulted in a therapeutic effect. To maintain the double-blind, patients who did not experience or maintain at least 5% weight loss while on placebo were re-randomized to receive placebo. The co-primary efficacy endpoints were measured at Week 28, with the Week 56 weight endpoints being the first two secondary endpoints assessed in the closed testing procedure (Section 6.5.1).

6.5.1 Efficacy Endpoints in the Phase 3 Studies

The four Phase 3 studies employed the FDA-recommended co-primary endpoints of mean and categorical percent changes from baseline in body weight. In addition, various secondary endpoints such as changes in waist circumference and other weight-related cardiometabolic

parameters, including lipid and glycemic measures, were evaluated. Other secondary endpoints included patient-reported assessments of quality of life and control of eating. Study NB-304 assessed the effect of NB32 on glycemic control in overweight and obese patients with type 2 diabetes.

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

- The percent change from baseline in body weight at Week 56 for Studies NB-301, NB-302, and NB-304 and at Week 28 for Study NB-303.
- The proportion of patients who achieved a ≥5% decrease from baseline body weight at Week 56 for Studies NB-301, NB-302, and NB-304 and at Week 28 for Study NB-303.

Secondary endpoints included the following:

- Study NB-303: Percent change from baseline in body weight and the proportion of patients who achieved a ≥5% decrease from baseline body weight at Week 56
- The proportion of patients who achieved a ≥10% decrease from baseline in body weight.
- The change from baseline in waist circumference.
- The change from baseline in lipid parameters (high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides).
- The change from baseline in high-sensitivity C-reactive protein (hs-CRP).
- The change from baseline in systolic and diastolic blood pressure.
- The change from baseline in glucose, insulin and Homeostasis model assessment of insulin resistance (HOMA-IR).
- Study NB-304 only: Change from baseline in hemoglobin A1c (HbA1c) and the proportion of patients: (1) with HbA1c <6.5%; (2) with HbA1c <7.0%; (3) needing rescue medications; (4) needing a change in doses of oral antidiabetic agents; and (5) who discontinued due to poor glycemic control.
- The change from baseline in the Impact of Weight on Quality of Life (IWQOL)-Lite questionnaire (Kolotkin et al., 2001) to assess the effect of obesity on quality of life.
- The change from baseline in the Control of Eating (COE) questionnaire (Hill and Blundell, 2006), where Item #19 was prespecified in the closed testing procedure in 3 of the 4 studies. This item asked “Generally, how difficult has it been to control your eating?”
- The change from baseline in the Food Craving Inventory (FCI) questionnaire (White et al., 2002).
- The change from baseline in the IDS-SR questionnaire (Rush et al., 1996) to assess changes in mood or depressive symptoms.

In the four pivotal studies, the hypothesis testing of the secondary efficacy endpoints was conducted in a sequential, hierarchical manner (i.e., a closed testing procedure [CTP]) that

was prespecified in the statistical analysis plan for each study (Appendix 5). The CTP was structured as follows: if the null hypothesis for both co-primary endpoints was rejected at the two-sided significance level of 0.05, then testing of the secondary efficacy endpoints proceeded in a sequential step-down manner. Testing of the secondary endpoints continued provided the null hypothesis for the previously tested endpoint was rejected at the two-sided significance level of 0.05; otherwise, no further hypothesis testing was done.

In this document, for ease of review, secondary endpoint data are presented descriptively along with nominal p-values for completeness, irrespective of whether analyses were conducted according to the CTP. A summary of the secondary endpoints based on the CTP for each study can be found in Appendix 5, Table 57 (Study NB-301), Table 58 (Study NB-302), Table 58 (Study NB-303), and Table 60 (Study NB-304).

6.5.2 Statistical Considerations Related to Efficacy

As recommended by the FDA Guidance on weight management, the primary efficacy analyses were to be conducted on a modified intent-to-treat (mITT) analysis population. The mITT population (also referred to as the Full Analysis Set) included all randomized patients who had a baseline measurement and at least one post-baseline 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 as the last non-missing post-baseline measurement using the LOCF principle while on study drug (i.e., within 1 day after the date of last confirmed dose). In Study NB-303, to avoid any influence of the NB48 dose on the Week 56 results, the main Week 56 analyses employed a weighted method where patients re-randomized to NB48 were excluded and patients re-randomized to continue on NB32 were double-weighted in the analyses. All placebo- and NB32-treated patients who were not re-randomized were given a weighting of 1.

In general, continuous change from baseline to endpoint variables were analyzed using an analysis of covariance (ANCOVA) model and categorical variables were analyzed using a linear logistic regression model. For individual studies, unless otherwise specified, the model contained the main effects of treatment and study center with the baseline measurement as the covariate. For Study NB-304, HbA1c strata (≤8% or >8%), and pharmacotherapy strata (with or without sulfonylurea) were also included in statistical models. For analyses in which multiple studies were pooled, the model contained the main effects of treatment and study identifier with the baseline measurement as the covariate.

Upon examination of the distribution for secondary efficacy variables, it was determined that the normality assumption underlying general linear models would not be met for fasting triglycerides, insulin, HOMA-IR, and hs-CRP. In order to more accurately assess the treatment effects, a log10 transformation of the ratio of endpoint to baseline (i.e., the difference of log10 transformation of the endpoint minus log10 transformation of the baseline) was used as the dependent variable in an ANCOVA model. Least squares means for each treatment group and least square treatment difference were calculated by back-transformation and presented as least squares mean percent change.

A panel of sensitivity analyses was conducted to support the robustness of the co-primary efficacy endpoints, as described below.

- BOCF: An analysis using all randomized patients in which endpoint was defined as the Week 56 measurement, irrespective of being on study drug or not (Week 28 for Study NB-303). For randomized patients who discontinued study drug prior to Week 56 (or Week 28 for Study NB-303), endpoint was the baseline measurement (i.e., the percent change from baseline was equal to zero for these patients). In other words, patients who dropped out early were classified as treatment failures for the primary endpoint of ≥5% weight loss from baseline and classified as having no weight change for the primary endpoint of percent change from baseline in body weight.
- Weight regain imputation method: An imputation method was used to account for missing values due to drop-outs, similar to Sacks, et al. (2009). For randomized patients who withdrew from the study early, weight was imputed assuming a 0.3 kg regain per month from the time of study withdrawal until either Week 56 or when the imputed weight reached the baseline weight, whichever occurred first. For patients who did not return after enrollment, their baseline was imputed for all missing values (i.e., the percent change from baseline was equal to zero for these patients). When a patient's weight at dropout represented a gain in weight relative to baseline, no additional gain will be imputed, and the last observation was carried forward.
- ITT analysis: This analysis included all randomized patients with a baseline and post-baseline body weight measurement where baseline was defined in the same manner described above and endpoint was defined as the last non-missing post-baseline measurement during the double-blind treatment phase (irrespective of being on study drug at the time of the last measurement).
- Repeated measures mixed effects model: An analysis of percent change (and change) from baseline on total body weight was performed using a repeated measures linear mixed-effects model. The model was implemented for the mITT and ITT populations. The model included as the dependent variable the percent change in total body weight from baseline measured at each of the planned monthly visits. Imputation of missing data was not performed for this analysis. The model included random subject effects, fixed class effects for treatment, time (i.e., week), the treatment-by-time interaction, study center (except for NB-304), and the baseline measurement as the covariate. For Study NB-304, HbA1c strata (≤8% or >8%), and pharmacotherapy strata (with or without sulfonylurea) were also included in the model.
- Completers analysis: For Studies NB-301 and NB-304, this analysis set included all randomized patients with a baseline measurement, a post-baseline body weight measurement, and who completed 56 weeks of treatment; for Study NB-303, the analysis was conducted in two sets of completers (Week 28 completers and Week 56 completers). For Study NB-302, the completer analysis set included all randomized patients who had a baseline measurement and a post-baseline measurement at Week 56 while on study drug (i.e., active treatment).

6.6 Patient Disposition and Analysis Population

Across the pivotal Phase 3 studies, a total of 8083 patients were screened, of whom 3547 (44%) failed screening and were not enrolled. Screen failure rates by study ranged from 33% (Study NB-303) to 69% (Study NB-304). The most frequent reasons for screen failure were clinical laboratory or vital signs values that were outside of the prespecified range. Study NB-304 had the highest screen failure rate in part due to difficulty in finding patients who met the HbA1c inclusion criterion (values between 7% and 10%).

Table 6 Number of Patients Screened and Screen Failure Rates by Phase 3 Study

	NB-301	NB-303	NB-302 BMOD	NB-304 T2DM
Total Number of Patients Screened, n	2929	2237	1292	1625
Screen Failures, n (%)	1187 (41)	741 (33)	499 (39)	1120 (69)

Abbreviations: BMOD=behavioral modification; T2DM=type 2 diabetes mellitus

Across the four Phase 3 studies, once randomized, 91% to 98% were included in the ITT analysis population, 81% to 96% were included in the mITT analysis population, 49% to 59% of patients were included in the completers analysis population (Table 7); the study completion results are generally comparable to other obesity trials (Padwal and Majumdar, 2007). Placebo-treated patients tended to discontinue more frequently due to lack of efficacy, withdrawal of consent, or lost to follow-up while NB-treated patients tended to discontinue more often due to AEs; a discussion of AEs leading to discontinuation is located in Section 7.4.4. Flow charts of patient disposition for the four Phase 3 studies are provided in Appendix 6.

Table 7 Analysis Populations and Patient Disposition by Phase 3 Study

Variable	NB-301			NB-303		NB-302 BMOD		NB-304 T2DM	
	PBO	NB16	NB32	PBO	NB32	PBO	NB32	PBO	NB32
Randomized (N)	581	578	583	495	1001	202	591	170	335
ITT, n (%)	536 (92.3)	524 (90.7)	538 (92.3)	474 (95.8)	943 (94.2)	196 (97.0)	565 (95.6)	166 (97.6)	321 (95.8)
mITT, n (%)	511 (88.0)	471 (81.5)	471 (80.8)	456 (92.1)	825 (82.4)	193 (95.5)	482 (81.6)	159 (93.5)	265 (79.1)
Completers, n (%)	290 (49.9)	284 (49.1)	296 (50.8)	267 (53.9)	538 (53.7)	106 (52.5)	301 (50.9)	100 (58.8)	175 (52.2)
Reason for Discontinuation, n (%)									
Adverse event	56 (9.6)	122 (21.1)	112 (19.2)	68 (13.7)	241 (24.1)	25 (12.4)	150 (25.4)	26 (15.3)	98 (29.3)
Withdrew consent	90 (15.5)	63 (10.9)	60 (10.3)	56 (11.3)	75 (7.5)	24 (11.9)	43 (7.3)	15 (8.8)	21 (6.3)
Lost to follow-up	66 (11.4)	76 (13.1)	65 (11.1)	48 (9.7)	77 (7.7)	17 (8.4)	22 (3.7)	15 (8.8)	22 (6.6)
Insufficient weight loss	40 (6.9)	12 (2.1)	12 (2.1)	33 (6.7)	19 (1.9)	6 (3.0)	3 (0.5)	6 (3.5)	5 (1.5)
Other[a]	39 (6.7)	21 (3.6)	38 (6.5)	23 (4.6)	51 (5.1)	12 (5.9)	31 (5.2)	8 (4.7)	14 (4.2)

a. Other includes: drug non-compliance, enrolled but did not meet selection criteria, failure to comply with protocol requirements, patient became pregnant, patient moved, and randomized but study drug not dispensed, other primary reason not listed, and death.

Abbreviations: BMOD=behavioral modification; PBO=placebo; T2DM=type 2 diabetes mellitus.

6.7 Study Populations

Demographic and baseline characteristics of the study population (randomized patients) across the four Phase 3 studies are summarized in Table 8. In general, there were no important or unexpected differences in demographic and baseline characteristics across treatment groups. Patients with diabetes had a slightly higher mean weight at baseline (105 kg), and higher proportions of patients with diabetes had baseline hypertension (62%) and dyslipidemia (84%).

The demographic and baseline characteristics of the mITT and study completer populations were similar to those described above for all randomized patients.

In general, the demographic and baseline characteristics of the Phase 3 study population are representative of the treatment-seeking segment of the obese and overweight population (Cawley and Rizzo, 2004).

Table 8 Patient Demographics and Other Baseline Characteristics by Phase 3 Study (Randomized Patients)

Variable	NB-301 (N=1742)	NB-303 (N=1496)	NB-302 BMOD (N=793)	NB-304 T2DM (N=505)
Mean Age (years)	44	44	46	54
Sex (% female)	85	85	90	56
Race (%)				
Caucasian	75	84	70	79
African American	19	14	24	16
Other	6	3	6	5
Hispanic or Latino (%)	13	8	10	12
Mean Weight (kg)	100	100	101	105
Mean BMI (kg/m^2)	36	36	37	36
Hypertension (%)	21	21	16	62
Dyslipidemia Subgroup (%)	49	55	44	84
CV history (%)	25	26	21	66
Impaired Fasting Glucose (%)	25	27	22	NA
Depression history (%)	11	14	14	9
Current Smoker (%)	11	11	0	11
Alcohol Use (%)	43	45	44	33

Notes:
(1) Hypertension subgroup defined as patients diagnosed at baseline with hypertension or prescribed anti-hypertensive concomitant medications at baseline.
(2) Dyslipidemia subgroup defined as diagnosed at baseline with dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, low HDL or with at least one of the following values prior to first dose of study drug: triglyceride ≥200 mg/dL, LDL cholesterol ≥160 mg/dL, total cholesterol ≥240 mg/dL, HDL cholesterol <40 mg/dL.

Abbreviations: BMOD=behavioral modification; CV history=medical history of arrhythmia, ischemia-related events or hypertension, at baseline; Depression history=positive for history of depression during psychiatric history evaluation at baseline; NA=not applicable; T2DM=type 2 diabetes mellitus.

6.8 Effect on Weight Loss and Weight Management

6.8.1 Co-Primary Efficacy Endpoints

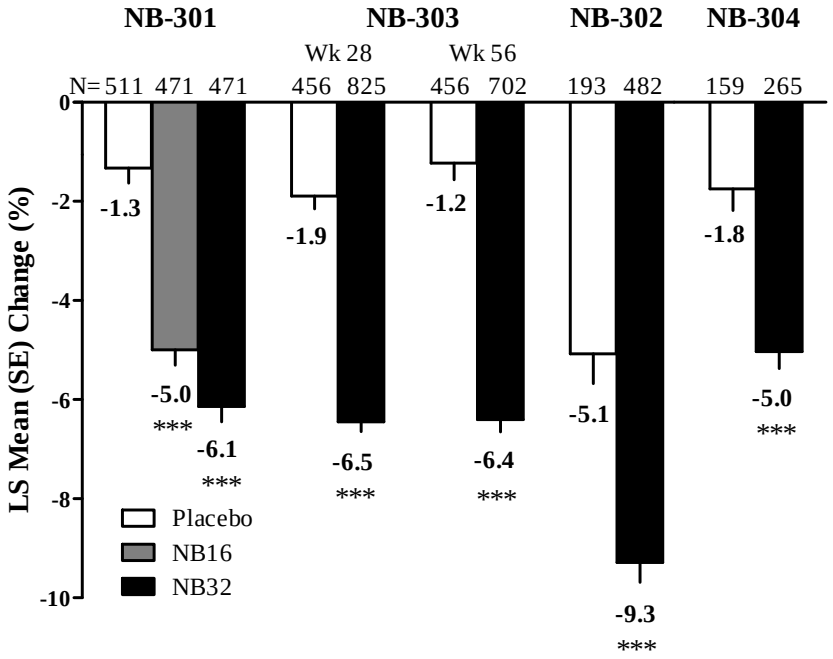
All four Phase 3 studies demonstrated statistically significant weight loss with NB32 (and NB16 in Study NB-301) compared with placebo in both co-primary endpoints in obese/overweight patients (Studies NB-301, NB-302, and NB-303) and in obese/overweight patients with type 2 diabetes mellitus (Study NB-304). To facilitate comparisons with the other three pivotal studies, discussion focuses on Week 56 data for Study NB-303; results at Week 28 (i.e., the primary endpoint) are comparable to Week 56 results (Figure 5 and Figure 6).

6.8.1.1 Percent Change in Body Weight from Baseline at Endpoint

In Studies NB-301 and NB-303, LS mean weight loss from baseline to Week 56 in NB32-treated patients was -6.1% and -6.4%, respectively, compared with -1.3% and -1.2%, respectively, in placebo-treated patients. As expected, greater percent change from baseline in total body weight was observed in patients undergoing intensive behavior modification counseling in Study NB-302 (-9.3% for NB32 and -5.1% for placebo), and smaller treatment effects were observed in obese/overweight patients with diabetes mellitus (Study NB-304: -5.0% for NB32 and -1.8% for placebo).

The LS mean differences from placebo in percent weight loss at Week 56 following treatment with NB32 were -4.8% for Study NB-301, -5.2% for Study NB-303, -4.2% for Study NB-302, and -3.3% for Study NB-304 (Figure 5).

Figure 5 Body Weight, Percent Change from Baseline to Endpoint by Phase 3 Study (mITT-LOCF)



Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis.
Abbreviations: LS mean=least squares mean; SE=standard error.
***p<0.001 vs. placebo

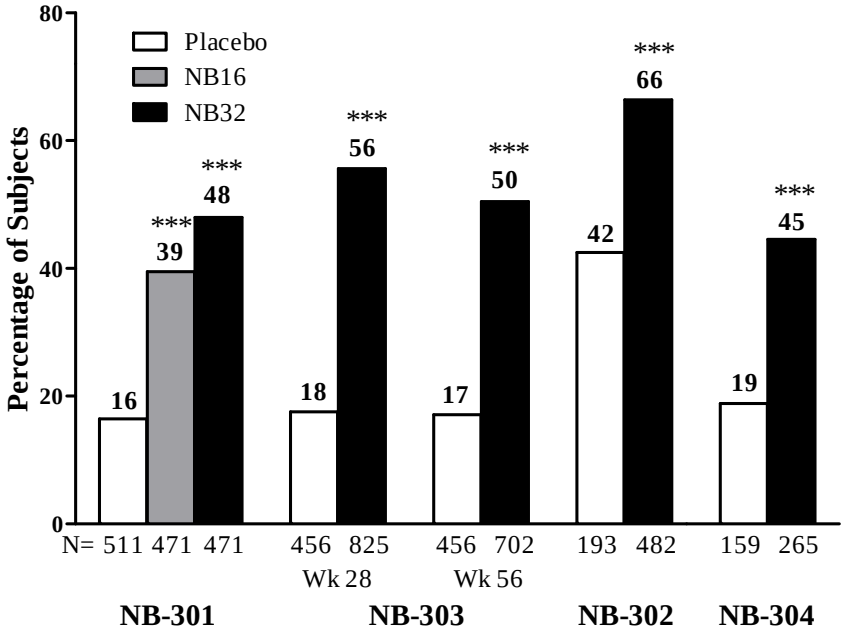
Unique design elements in each of the Phase 3 studies resulted in important study-specific efficacy findings.

- In Study NB-301, NB16 resulted in statistically superior efficacy compared with placebo, but was somewhat less efficacious than NB32. These results are comparable with those seen in Phase 2 Study NB-201 and provide further support to the hypothesis that mu-opioid receptor blockade induced by naltrexone potentiates the effects of bupropion on weight loss.
- In Study NB-302, in the context of the intensive program of diet, exercise and counseling, treatment with NB32 resulted in greater weight loss from baseline compared with NB32 in the other Phase 3 studies; NB32 also yielded significantly greater weight loss than placebo treatment.
- In Study NB-303, treatment with NB48 provided no additional weight loss relative to NB32 in patients who failed to achieve or maintain a ≥5% reduction in body weight between Weeks 28 and 44.
- In Study NB-304, consistent with reports in the scientific literature (Khan et al., 2000), the effect of NB32 treatment was less pronounced compared with the results seen in non-diabetic patients.

6.8.1.2 Proportion of Patients with ≥5% Weight Loss

In Studies NB-301 and NB-303, the proportion of NB32-treated patients who achieved a clinically meaningful weight loss of ≥5% from baseline at Week 56 was 48% and 50%, respectively, compared with 16% and 17%, respectively, in placebo-treated patients (Figure 6). As expected, a higher proportion of patients achieved ≥5% weight loss from baseline in Study NB-302 (66% for NB32 and 42% for placebo), and smaller treatment effects were observed for NB32 in patients with diabetes mellitus (Study NB-304: 45% for NB32 and 19% for placebo).

Figure 6 Body Weight, Proportion of Patients with a ≥5% Decrease from Baseline to Endpoint by Phase 3 Study (mITT-LOCF)



Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis.
***p<0.001 vs. placebo. P-values are based on odds ratios.

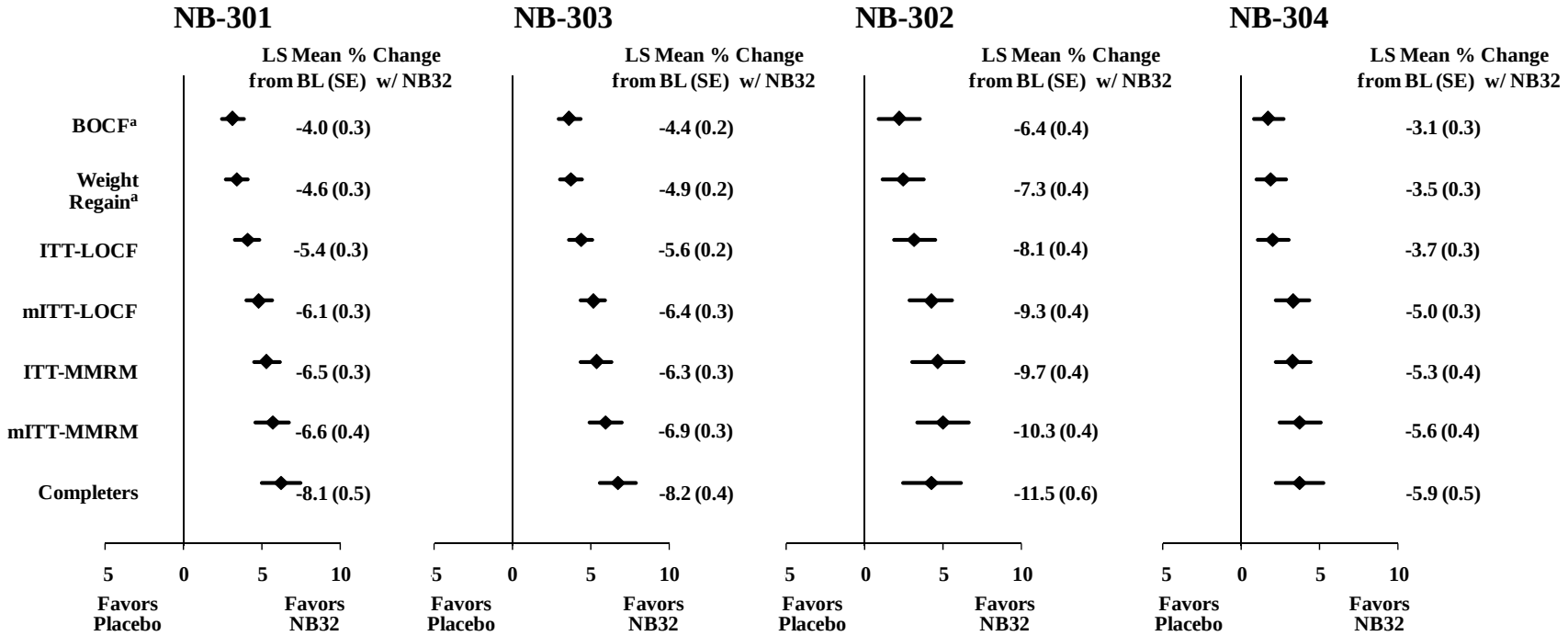
6.8.1.3 Co-Primary Endpoint Sensitivity Analyses

Sensitivity analyses (as defined in Section 6.5.2) were conducted on the co-primary efficacy measures to examine the robustness of the effect in the primary analyses and to address the potential bias associated with missing data due to early patient withdrawals. For consistency with the other three pivotal studies, Week 56 data are presented for Study NB-303; however, the results of the sensitivity analyses at Week 28 (i.e., the primary endpoint) are comparable to Week 56 results.

Figure 7 and Figure 8 present the results of the sensitivity analyses of the co-primary endpoints for each of the four pivotal studies; for comparison the results from the mITT analysis (i.e., the primary analysis set) are also included. The significant treatment effects on the mITT analysis set following treatment with NB32 were also observed for each sensitivity analysis employed, confirming the robustness of the results.

- In the two analyses that assumed either zero weight loss (BOCF) or weight regain following discontinuation of study drug (weight regain imputation method), clinically meaningful and statistically significant effects following treatment with NB32 were observed.
- Analyses on datasets that included patients with minimal exposure to study drug (ITT analysis set) also demonstrated robust effects following treatment with NB32.
- As expected, analyses where only observed data were used (ITT-mixed effect model of repeated measures [ITT-MMRM], mITT-MMRM, and the completers analyses) showed the greatest treatment effects on the percent weight loss, as well as the highest odds ratio of achieving a ≥5% weight loss from baseline.

Figure 7 Sensitivity Analyses, Placebo-Corrected Percent Change in Weight from Baseline to Week 56 Endpoint by Phase 3 Study

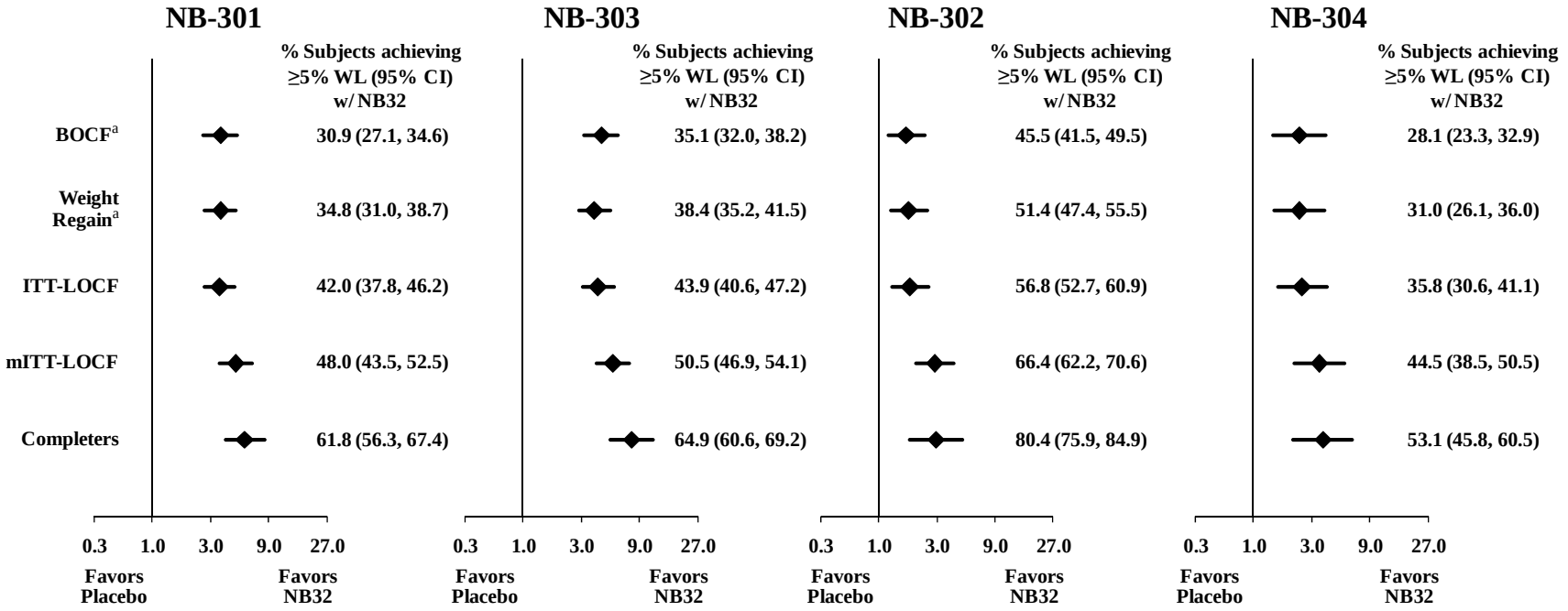


a. BOCF and weight regain analyses include all randomized patients.

Study NB-303 Week 56 endpoint results are based upon the weighted analysis; Data are LS mean difference from placebo and associated 95% CI; Because a negative treatment difference indicates improvement over placebo, the values are reversed so that the direction that favors NB32 remains constant.

Abbreviations: BOCF=baseline observation carried forward; CI=confidence interval; LS mean=least squares mean; MMRM=mixed effect model of repeated measures; SE=standard error.

Figure 8 Sensitivity Analyses, Odds Ratio of Achieving ≥5% Decrease in Weight from Baseline to Week 56 Endpoint by Phase 3 Study



a. BOCF and weight regain analyses include all randomized patients.

Study NB-303 Week 56 endpoint results are based upon the weighted analysis; Data are odds ratios and associated 95% CI.
Abbreviations: BOCF=baseline observation carried forward; CI=confidence interval; WL=weight loss.

6.8.1.4 FDA Guidance Efficacy Benchmarks

Based on the 2007 FDA Guidance on developing products for weight management, 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 treatment group and placebo is at least 5% and the difference is statistically significant;

  OR

- The proportion of patients who lose ≥5% of their baseline body weight in the active treatment group is at least 35%, is approximately double the proportion in the placebo group, and the difference between the active and placebo groups is statistically significant.

Studies NB-301, NB-303 and NB-304 met the ≥5% responder benchmark on the mITT analysis set, and each of these studies met the benchmark on at least two or more of the sensitivity analyses, including the BOCF and weight regain imputation methods in Study NB-303.

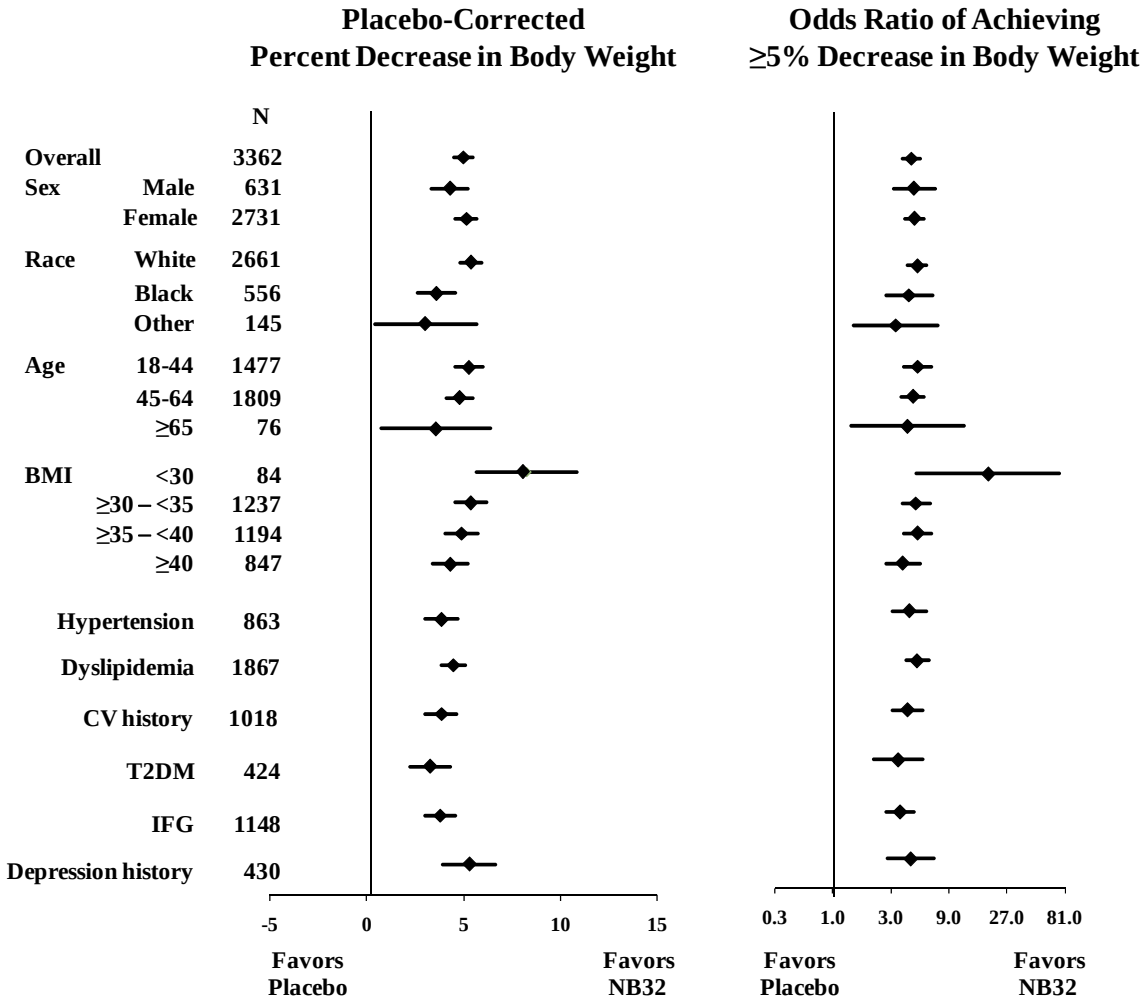
With regard to the mean percent weight loss efficacy benchmark, Study NB-303 met the benchmark at Week 56 for the mITT analysis set, and both Studies NB-301 and NB-303 met the benchmark on three of the Week 56 sensitivity analyses (ITT-MMRM, mITT-MMRM, and completers).

6.8.2 Weight Loss Efficacy in Subpopulations

Subgroup analyses were performed to examine how patient baseline demographic (sex, age, race, and baseline BMI) or disease characteristics (hypertension, dyslipidemia, CV history, type 2 diabetes, impaired fasting glucose, or history of depression) may influence NB-induced weight loss. The comparisons of pooled data (NB32 and placebo) across the four pivotal studies were analyzed for each subgroup for the co-primary endpoints (Figure 9). It should be noted that Study NB-303 patients re-randomized to NB32 or NB48 were included, thus no double-weighting was employed for the pooled analysis.

Although greater variability was noted in some of the smaller subsets, treatment with NB32 resulted in greater weight loss (based on mean percent weight loss at endpoint and odds ratio of achieving ≥5% weight loss at endpoint) compared with placebo treatment irrespective of sex, race, age, baseline BMI, or presence of hypertension, dyslipidemia, a history of cardiovascular disease, type 2 diabetes, impaired fasting glucose or history of depression at baseline.

Figure 9 Subgroup Analyses, Co-Primary Endpoints for all Phase 3 Studies (Pooled) (mITT-LOCF)



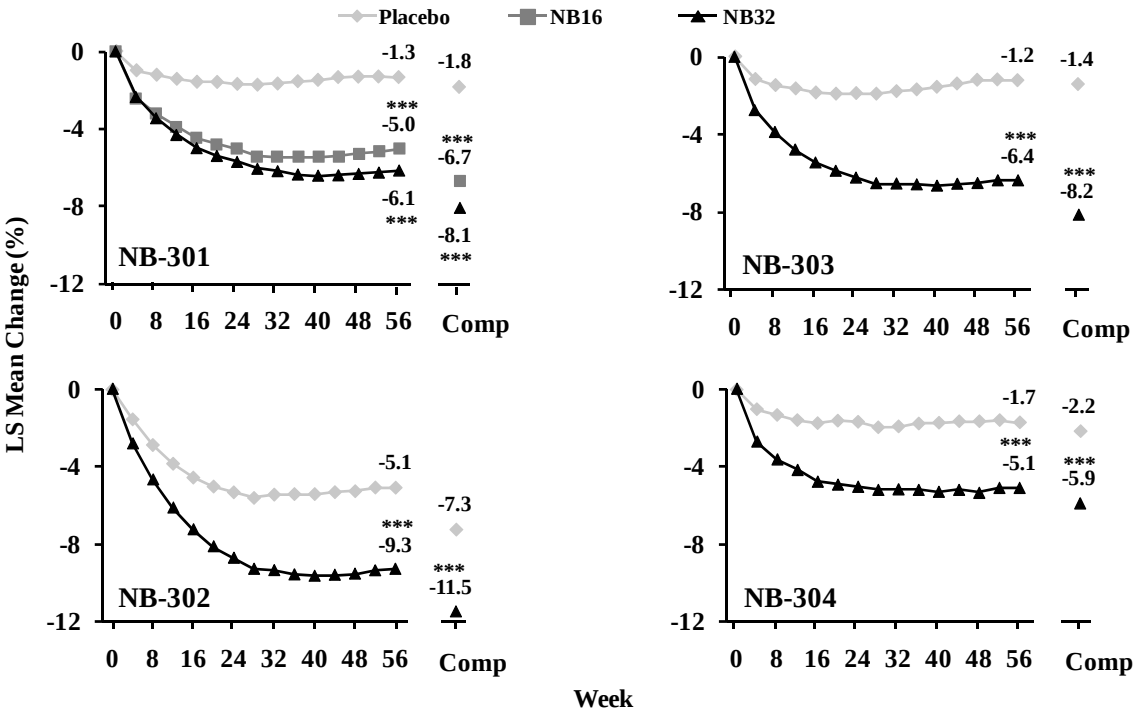
Data for percent decrease in body weight are LS mean difference from placebo for baseline to Week 56 endpoint and associated 95% CI; Data for ≥5% decrease in body weight are odds ratios of achieving ≥5% weight loss at Week 56 endpoint and associated 95% CI; Because a negative treatment difference indicates improvement over placebo, the values are reversed for placebo-corrected percent decrease in body weight so that the direction that favors NB32 remains constant; patients may be counted in more than one subgroup.
Abbreviations: BMI=body mass index; CI=confidence interval; CV history=medical history of arrhythmia, ischemia-related events or hypertension, at baseline; Depression history=positive for history of depression during psychiatric history evaluation at baseline; Dyslipidemia=diagnosed with dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, low HDL or had triglycerides ≥200 mg/dL, LDL-C ≥160 mg/dL, total cholesterol ≥240 mg/dL, or HDL-C <40 mg/dL at baseline; Hypertension=diagnosed with hypertension or had prescribed anti-hypertensive medications at baseline; IFG=fasting glucose ≥100 mg/dL at baseline; N=NB32+placebo patients; T2DM=type 2 diabetes mellitus.

6.8.3 Percent Weight Loss Over Time

Percent weight loss over time across the four pivotal Phase 3 studies is depicted in Figure 10. In comparison with placebo treatment, greater weight loss, beginning as early as Week 4, was observed in patients receiving NB treatment. Maximum weight loss was achieved after approximately 28 to 40 weeks of NB treatment, and the weight loss associated with NB32 treatment was maintained throughout the duration of the studies. The subset of patients who continued NB32 treatment through Week 56 experienced the greatest magnitude of weight

loss. The weight loss pattern was similar when evaluated using a BOCF imputation and in the completer subset.

Figure 10 Body Weight, Percent Change from Baseline to Each Visit by Phase 3 Study (mITT-LOCF)

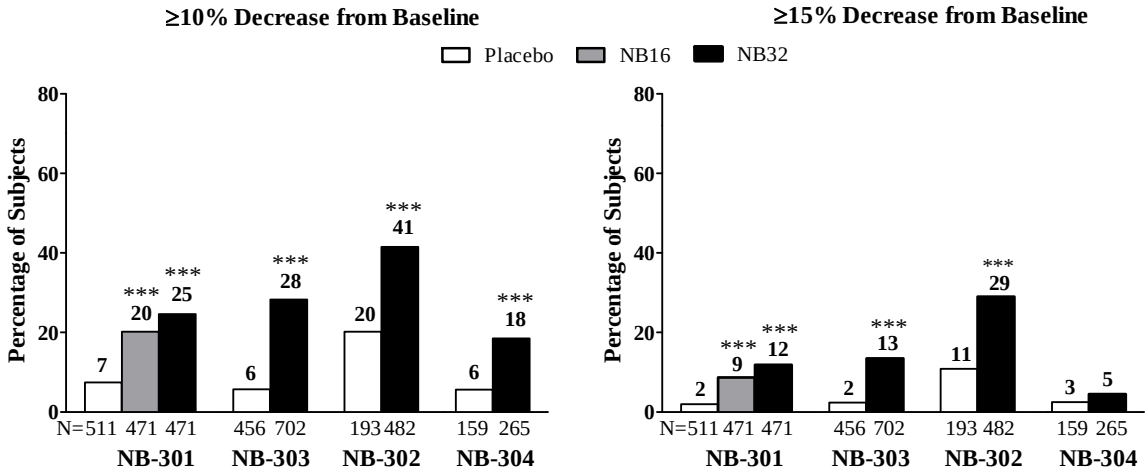


Study NB-303 results for Weeks 28 through endpoint are based upon the weighted LOCF analysis.
Abbreviations: comp=completers at Week 56 endpoint; LS mean=least squares mean.
***p<0.001 vs. placebo.

6.8.4 Proportion of Patients Achieving a ≥10% and a ≥15% Weight Loss

The proportion of patients who met the more stringent categorical weight loss criteria of ≥10% weight loss at Week 56 following NB32 treatment was consistently higher than following placebo treatment (Figure 11). Greater NB treatment effects were also observed for the proportion of patients with ≥15% weight loss from baseline (except in Study NB-304).

Figure 11 Body Weight, Proportion of Patients with ≥ 10% and ≥ 15% Decrease from Baseline to Week 56 Endpoint by Phase 3 Study (mITT-LOCF)

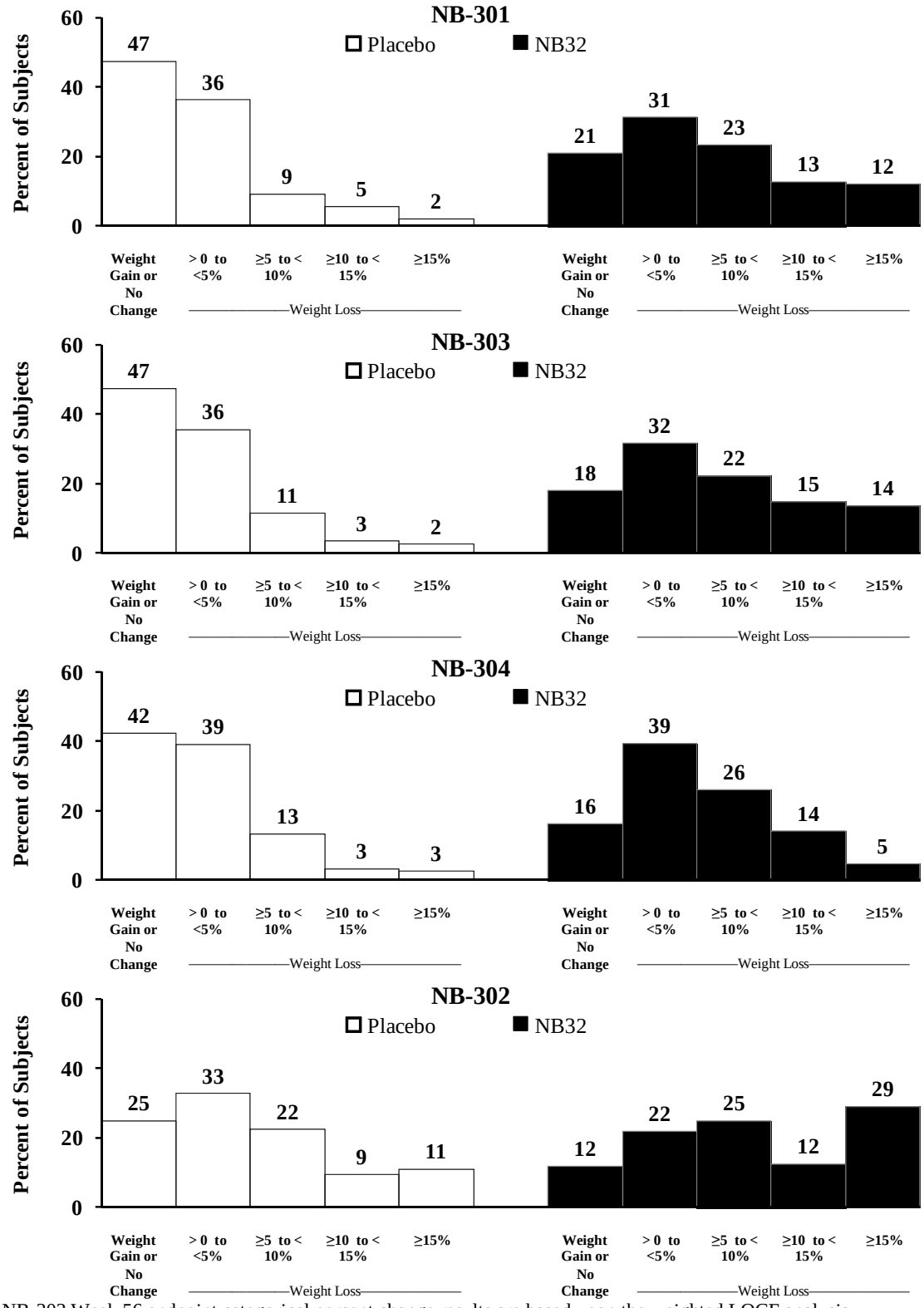


Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis.
***p<0.001 vs. placebo. P-values are based on odds ratios.

6.8.5 Distribution of Weight Change

A graphical summary of the distribution of percent weight change by category in each of the four pivotal studies is presented in Figure 12.

Figure 12 Proportion of Patients with Categorical Percent Weight Change from Baseline to Week 56 Endpoint (mITT-LOCF)



Study NB-303 Week 56 endpoint categorical percent change results are based upon the weighted LOCF analysis.

6.9 Secondary Efficacy Measures

In addition to the demonstration of weight loss and the maintenance of weight loss, secondary efficacy measures employed in the NB Phase 3 program allowed for an assessment of the efficacy of NB on:

- Weight-related cardiometabolic parameters (e.g., waist circumference, lipids, hs-CRP, and blood pressure) and body composition
- Glycemic control (e.g., fasting glucose, fasting insulin, HOMA-IR, and, in patients with diabetes, HbA1c)
- Quality of life (IWQOL-Lite scale)
- Control of eating
- Effects of treatment on the IDS-SR score; discussed in the safety section (see Section 7.6.3.1.1)

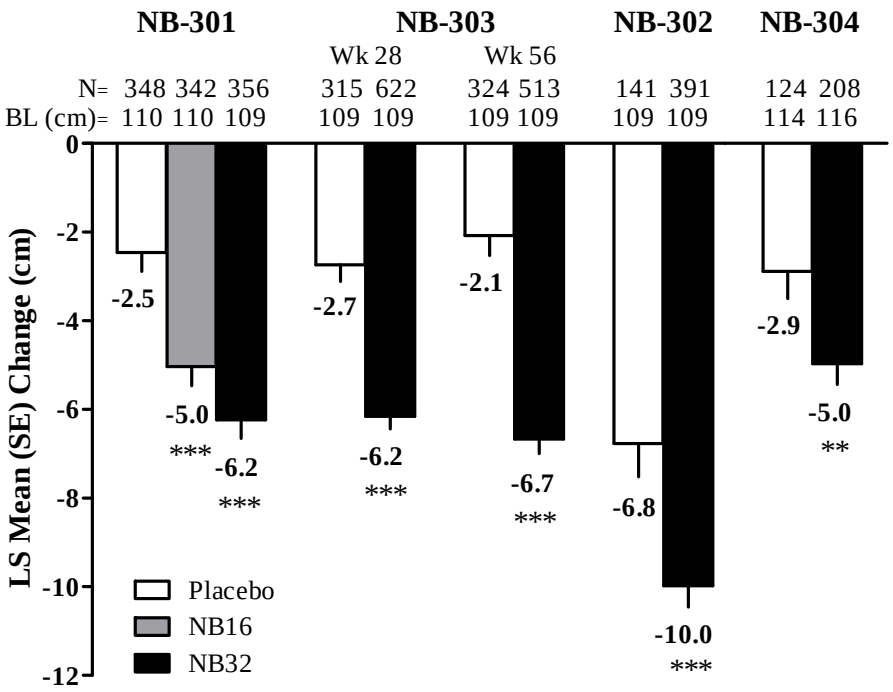
6.9.1 Weight-related Cardiometabolic Parameters

Across the four Phase 3 studies, treatment with NB32 (and NB16 in Study NB-301) resulted in statistically significant and clinically meaningful improvements on multiple weight-related cardiometabolic parameters.

6.9.1.1 Waist Circumference

At baseline, mean waist circumference ranged from 109 to 116 cm across the studies and was balanced between treatment groups. Treatment with NB32 across the four Phase 3 studies (and NB16 in NB-301) resulted in consistently greater reductions from baseline in waist circumference compared with placebo (Figure 13). Week 56 LS mean differences from placebo were -3.8 cm in NB-301 (for NB32), -4.6 cm in NB-303, -3.2 cm in NB-302, and -2.1 cm in NB-304.

Figure 13 Waist Circumference, Change from Baseline to Endpoint by Phase 3 Study (mITT-LOCF)



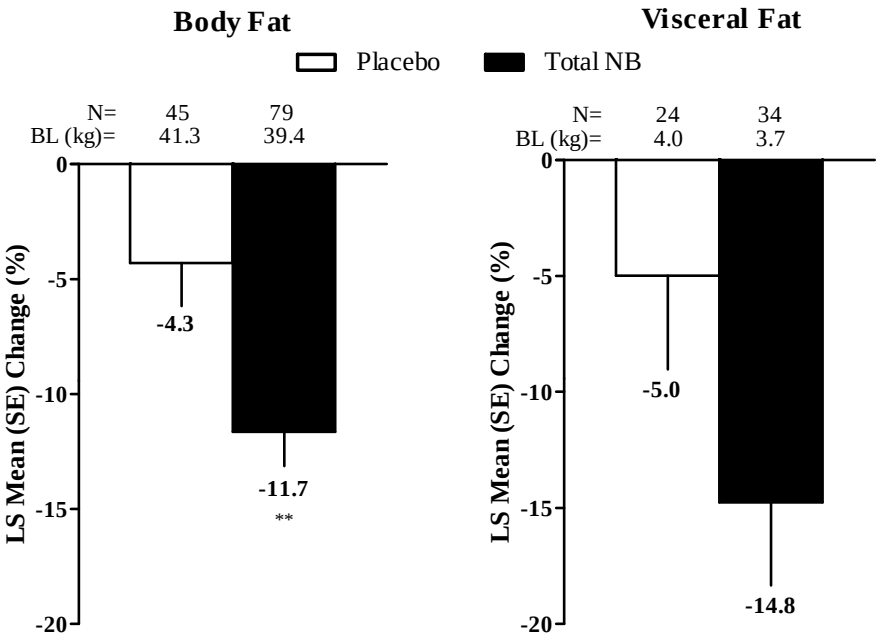
Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis.
Abbreviations: BL=mean baseline; LS mean=least squares mean; SE=standard error.
***p<0.001, **p<0.01 vs. placebo

6.9.1.1.1 Effect on Body Composition

In order to better characterize the effect on body composition of NB treatment, a subset of Study NB-301 investigative sites also evaluated study participants with dual energy x-ray absorptiometry (DEXA) and abdominal computed tomography (CT) scans at baseline and endpoint.

As presented in Figure 14, treatment with NB was associated with greater reductions from baseline in total body fat (NB: -11.7%; placebo: -4.3%; p<0.01) and in visceral adipose tissue (NB: -14.8%; placebo: -5.0%; p=0.069) than placebo. Not unexpectedly, NB-treated patients had a greater mean *increase* from baseline compared with placebo-treated patients in percent of total body lean mass (NB: 2.44%; placebo: 0.77%; p=0.006). These results indicate that most of the total weight loss was attributable to a reduction in adipose tissue, including visceral adipose. Treatment with NB also resulted in a greater reduction in hepatic lipid content compared with placebo treatment (data not shown).

Figure 14 Body Fat and Visceral Adipose Tissue, Percent Change from Baseline to Week 52 Endpoint in NB-301 Substudy (mITT-LOCF)



Abbreviations: BL= mean baseline; LS mean=least squares mean; Total NB=NB16 and NB32 pooled; SE=standard error.
**<0.01 vs. placebo

6.9.1.2 Lipid Parameters

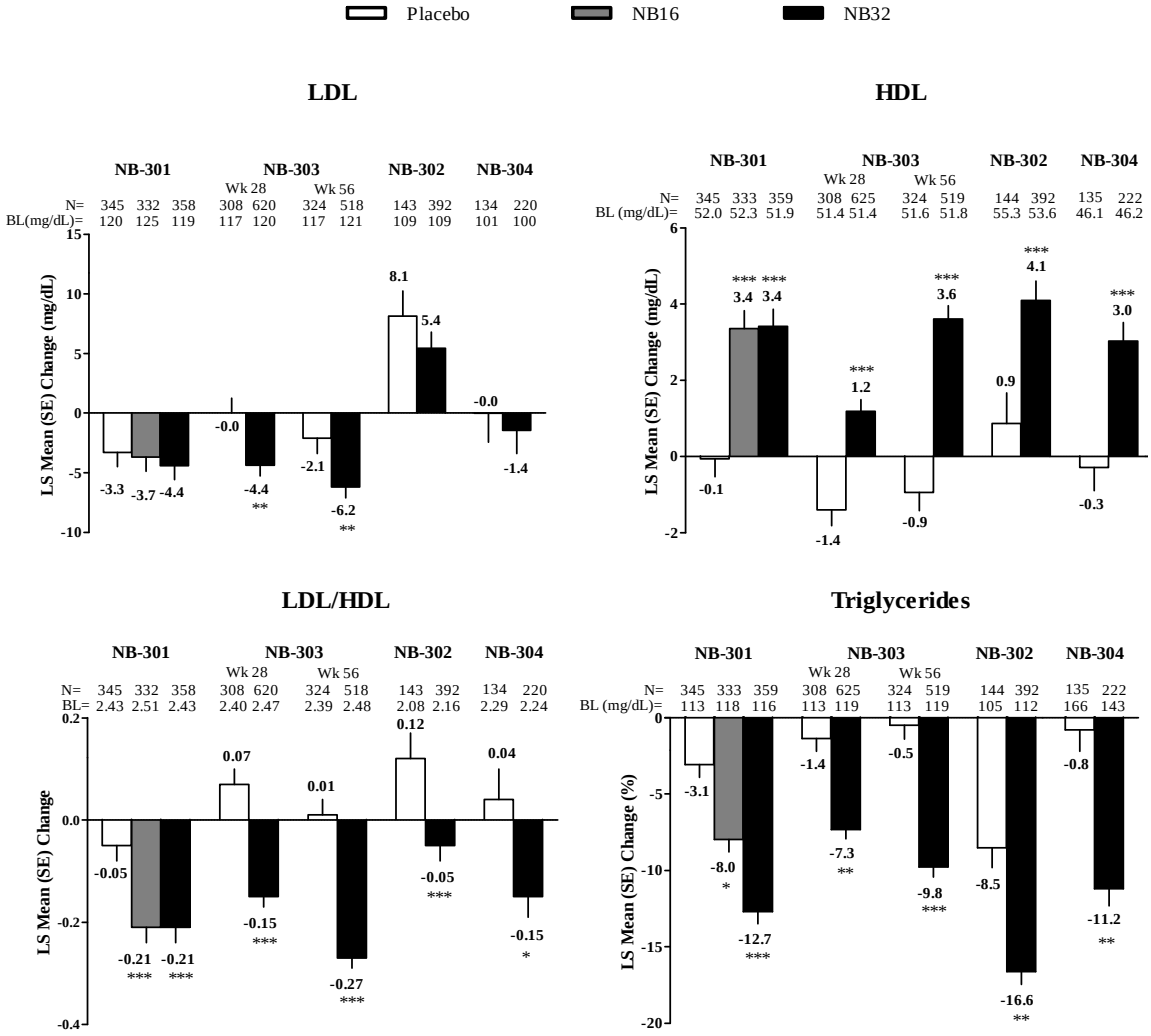
Treatment with NB32 (and NB16 in Study NB-301) resulted in an improved lipid profile in overweight and obese patients. Similar to results described in the obesity literature (Wirth and Krause, 2001; Després et al., 2005) regarding the effects of weight loss agents on metabolic parameters, the most prominent changes in patients receiving NB32 were on fasting triglyceride levels and fasting HDL.

- At baseline, fasting triglyceride levels ranged from 105 to 166 mg/dL across the studies and were balanced between treatment groups. Treatment with NB32 across the four Phase 3 studies (and NB16 in NB-301) resulted in consistently greater percent reductions from baseline in triglycerides compared with placebo (Figure 15). Week 56 LS mean differences from placebo were -9.6% in NB-301 (for NB32), -9.3% in NB-303, -8.1% in NB-302, and -10.4% in NB-304.
- At baseline, fasting HDL levels ranged from 46 to 55 mg/dL across the studies and were balanced between treatment groups. Treatment with NB32 across the four Phase 3 studies (and NB16 in NB-301) resulted in consistently greater increases from baseline in HDL levels compared with placebo (Figure 15). Week 56 LS mean differences from placebo were 3.5 mg/dL in NB-301 (for NB32), 4.6 mg/dL in NB-303, 3.2 mg/dL in NB-302, and 3.3 mg/dL in NB-304.

Similar to previous findings with other weight loss regimens (Wirth and Krause, 2001; Després et al., 2005), LDL levels were largely unchanged from baseline across the four studies.

- At baseline, fasting LDL levels ranged from 100 to 125 mg/dL across the studies and were relatively balanced between treatment groups. Treatment with NB32 across the four Phase 3 studies (and NB16 in NB-301) resulted in small decreases from baseline in LDL levels compared with placebo (Figure 15). Week 56 LS mean differences from placebo were -1.1 mg/dL in NB-301 (for NB32), -4.1 mg/dL in NB-303, -2.7 mg/dL in NB-302, and -1.4 mg/dL in NB-304.
- Decreases in the LDL to HDL ratio were observed at endpoint in NB32-treated patients in each of the four pivotal studies, primarily due to increases in HDL (Figure 15).

Figure 15 Lipid Parameters, Change from Baseline to Endpoint by Phase 3 Study (mITT-LOCF)



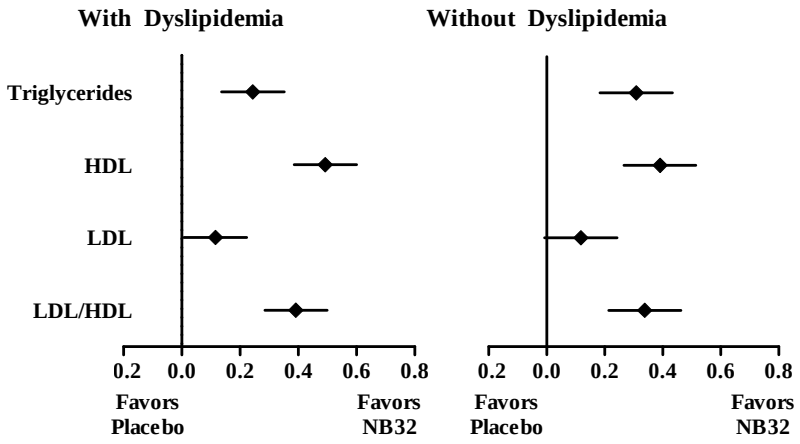
***p<0.001, **p<0.01, *p<0.05 vs. placebo. Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis; for triglycerides, analysis used log-transformed data and baseline data are geometric mean.
Abbreviations: BL=mean baseline unless specified otherwise; HDL=high-density lipoproteins; LDL=low-density lipoproteins; LS mean=least squares mean; SE=standard error.

6.9.1.2.1 Effect of NB on Lipid Parameters in Subpopulations

Subgroup analyses were performed to examine whether the presence of dyslipidemia at baseline or the use of medications for the treatment of dyslipidemia at baseline may influence the effects of NB treatment on lipid parameters. The comparisons of pooled data (NB32 and placebo) across the four pivotal studies were analyzed for each subgroup for the co-primary endpoints (Figure 16).

Consistent with the findings in the overall study population, clinically significant improvement associated with NB32 in HDL and triglycerides were observed in patients with and without dyslipidemia at baseline.

Figure 16 Effect Sizes from Baseline to Week 56 Endpoint for Lipids by Presence or Absence of Dyslipidemia at Baseline for all Phase 3 Studies (Pooled) (mITT-LOCF)

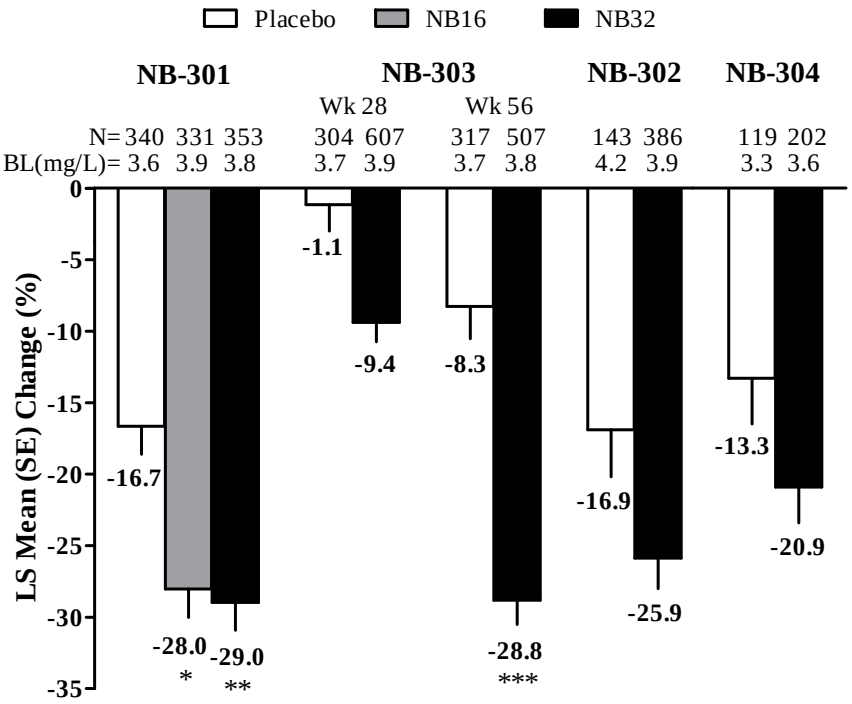


Analysis for triglycerides used log-transformed data; Data are effect sizes and associated 95% CI; For parameters where a negative treatment difference indicates improvement over placebo, the values are reversed so that the direction that favors NB32 remains constant.
Abbreviations: CI=confidence interval; HDL=high-density lipoproteins; LDL=low-density lipoproteins.

6.9.1.3 High-sensitivity C reactive protein

At baseline, hs-CRP values ranged from 3.3 to 4.2 mg/L across the studies and were balanced between treatment groups. Lower hs-CRP values may be associated with decreased CV risk (Ridker et al., 2008). As expected given the results on total body weight (Esposito et al., 2003), treatment with NB32 across the four Phase 3 studies (and NB16 in NB-301) resulted in consistently greater percent reductions from baseline in hs-CRP compared with placebo-treated patients (Figure 17). Week 56 LS mean differences from placebo were -12.3% in NB-301 (for NB32, $p<0.01$), -20.6% in NB-303 ($p<0.001$), -9.0% in NB-302, and -7.6% in NB-304.

Figure 17 hs-CRP, Percent Change from Baseline to Endpoint by Phase 3 Study (mITT-LOCF)



Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis; Analysis used log-transformed data.

Abbreviations: BL=geometric mean baseline; LS mean=least squares mean; SE=standard error.

***p<0.001, **p<0.01, *p<0.05 vs. placebo

6.9.1.4 Blood Pressure

Across the four Phase 3 studies, the LS mean changes from baseline to endpoint in SBP in NB32-treated patients ranged from -1.3 to +0.6 mm Hg; similar LS mean changes from baseline to endpoint were observed in DBP (-1.4 to +0.4 mm Hg). Placebo-treated patients displayed greater LS mean decreases from baseline in blood pressure (-3.9 to -0.5 mm Hg for SBP and -2.8 to +0.3 mm Hg for DBP).

A pooled analysis across the Phase 3 studies of mean changes in SBP (Figure 32) and DBP (Figure 33) by weight loss category indicates greater decreases from baseline in SBP and DBP in patients experiencing greater degrees of weight loss. Placebo-treated patients experienced greater reductions within each weight loss category compared with NB32-treated patients.

Effects of treatment on systolic and diastolic blood pressure and pulse are discussed in detail in Section 7.6.1.

6.9.2 Glycemic Control

6.9.2.1 Glycemic Control in Patients with Diabetes

Study NB-304 evaluated the efficacy and safety of NB32 compared with placebo in the treatment of obese/overweight patients with type 2 diabetes mellitus.

In order to participate in Study NB-304, patients were required to have an HbA1c between 7% and 10%, fasting blood glucose <270 mg/dL, and fasting triglycerides <400 mg/dL. Overall, the results from Study NB-304 indicate that the effects of NB therapy on weight loss are also associated with clinically significant improvements in glycemic control in obese/overweight patients with type 2 diabetes mellitus.

Patients were permitted to be on single or combination oral antidiabetic medications (biguanides [metformin], thiazolidinediones, meglitinides, α-glucosidase inhibitors, sulfonylureas, DPP4 inhibitors) as long as the medication had been stable for at least 3 months prior to randomization; patients were not permitted to have taken injectable antidiabetic medications or inhaled insulin for more than 3 months prior to randomization. At baseline, the use of oral antidiabetic medications between NB32- and placebo-treated patients was comparable; the most commonly used single or combination antidiabetic medications are summarized in Table 9.

Table 9 Percent of Patients Using Antidiabetic Medications at Baseline: Study NB-304, mITT

Antidiabetic Medication	Placebo (N=159)	NB32 (N=265)
Biguanides, alone or in combination	76.7%	79.6%
Sulfonylurea, alone or in combination	49.1%	49.1%
Thiazolidinedione, alone or in combination	31.4%	31.3%
Biguanide+Thiazolidinedione+Sulfonylurea	13.8%	15.5%
Biguanide+Thiazolidinedione	12.6%	11.3%
Biguanide+ Sulfonylurea	25.8%	27.2%
Thiazolidinedione+Sulfonylurea	3.1%	0.8%
Biguanide only	24.5%	25.7%
Thiazolidinedione only	1.9%	3.8%
Sulfonylurea only	6.3%	5.7%
None of the above	11.9%	10.2%

During Weeks 1 through 16 of Study NB-304, adjustment or addition of antidiabetic medications was discouraged to allow study interventions (including dietary and lifestyle modifications) the opportunity to improve patients' glycemic control. Indications for adjustment of antidiabetic medications included HbA1c values >9.5% at Week 16 or subsequent visits, any post-baseline HbA1c ≥10.0%, and two or more successive post-baseline fasting glucose concentrations ≥270 mg/dL.

Before adding a new antidiabetic medication, full doses of metformin (≥1500 mg/day) or sulfonylurea (glyburide ≥10 mg/day, glipizide ≥20 mg/day) were to have been used. The

dose of antidiabetic medications did not exceed the FDA-approved maximum recommended dose.

When additional antidiabetic medication was necessary, the following sequence was recommended:

Current Uncontrolled Antidiabetic Therapy	Suggested Additional Antidiabetic Therapy
Diet	Metformin
Metformin	Sulfonylurea (Including Meglitinides)
Sulfonylurea	Metformin
Metformin + Sulfonylurea	DPP-4 Inhibitor or Thiazolidinedione

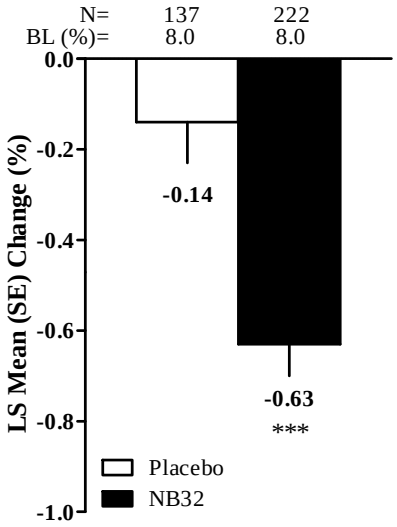
Alternative oral antidiabetic medication combinations were considered at the discretion of the investigator. Patients who required insulin therapy for greater than 14 consecutive days were discontinued from the study.

Patients who experienced improvement in glycemic control during study participation and required a reduction in dosage or discontinuation of an antidiabetic medication were recommended to do so in reverse order to the sequence described above.

Change from Baseline in HbA1c

In Study NB-304, statistically and clinically significant treatment effects were observed with NB32 therapy on HbA1c. At baseline , HbA1c was 8.0% for both the NB32 and placebo treatment groups. At Week 56, NB32-treated patients experienced a -0.63% reduction in HbA1c compared with a -0.14% reduction in placebo-treated patients (p<0.001; Figure 18).

Figure 18 HbA1c, Change from Baseline to Week 56 Endpoint in Study NB-304 (mITT-LOCF)

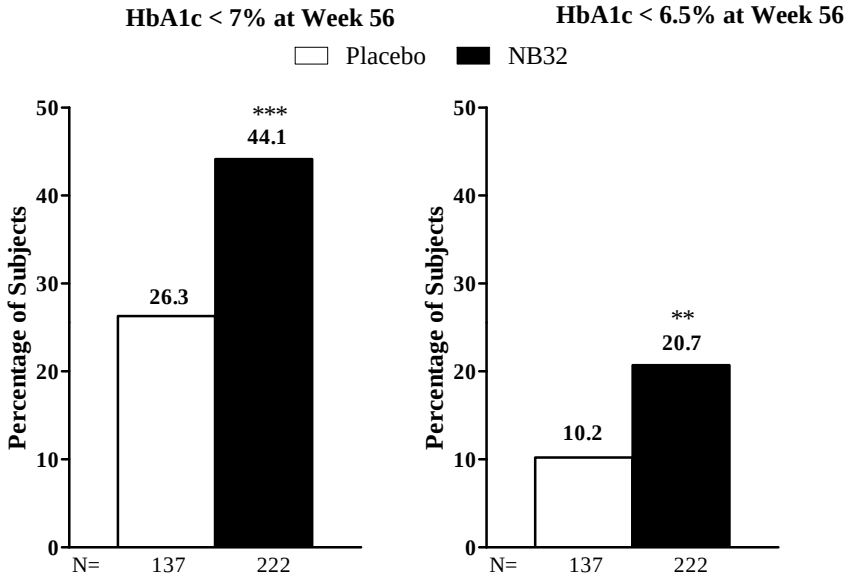


Abbreviations: BL=mean baseline; LS mean=least squares mean; SE=standard error.
***p<0.001 vs. placebo

Proportion of Patients Achieving HbA1c Values of <7% and <6.5%

As shown in Figure 19, a higher proportion of NB32-treated patients achieved HbA1c values <7% (44.1%) and <6.5% (20.7%) compared with placebo-treated patients (<7%: 26.3%, and <6.5%: 10.2%).

Figure 19 HbA1c, Proportion of Patients with <7% and <6.5% at Week 56 Endpoint in Study NB-304 (mITT-LOCF)

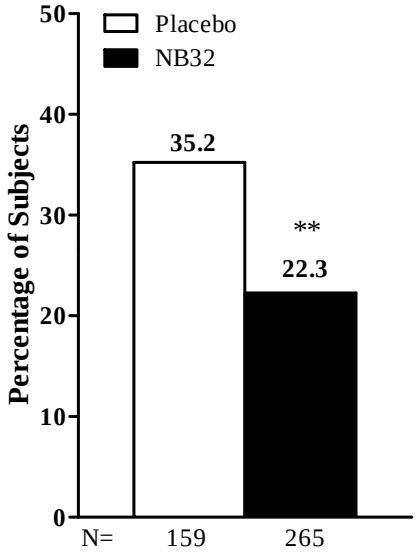


***p<0.001, **<0.01 vs. placebo. P-values are based on odds ratios.

Use of Rescue Medications for Glycemic Control

In Study NB-304, a lower proportion of NB32-treated patients required rescue medications [additional antidiabetic medications or increases in the dose(s) of their current antidiabetic medication(s)] compared with placebo-treated patients (NB32: 22.3%; placebo: 35.2%; p<0.01; Figure 20).

Figure 20 Proportion of Patients Requiring Rescue Medications for Glycemic Control During Study NB-304 (mITT-LOCF)



**<0.01 vs. Placebo. P-values are based on odds ratios.

Change from Baseline in Fasting Glucose, Fasting Insulin, and HOMA-IR

In Study NB-304, NB32, compared with placebo, resulted in numerically greater improvements at Week 56 in fasting glucose (NB32: -11.9 mg/dL; placebo: -4.0 mg/dL), fasting insulin (NB32: -13.5%; placebo: -10.4%) and HOMA-IR (NB32: -20.6%; placebo: -14.7%; Figure 21).

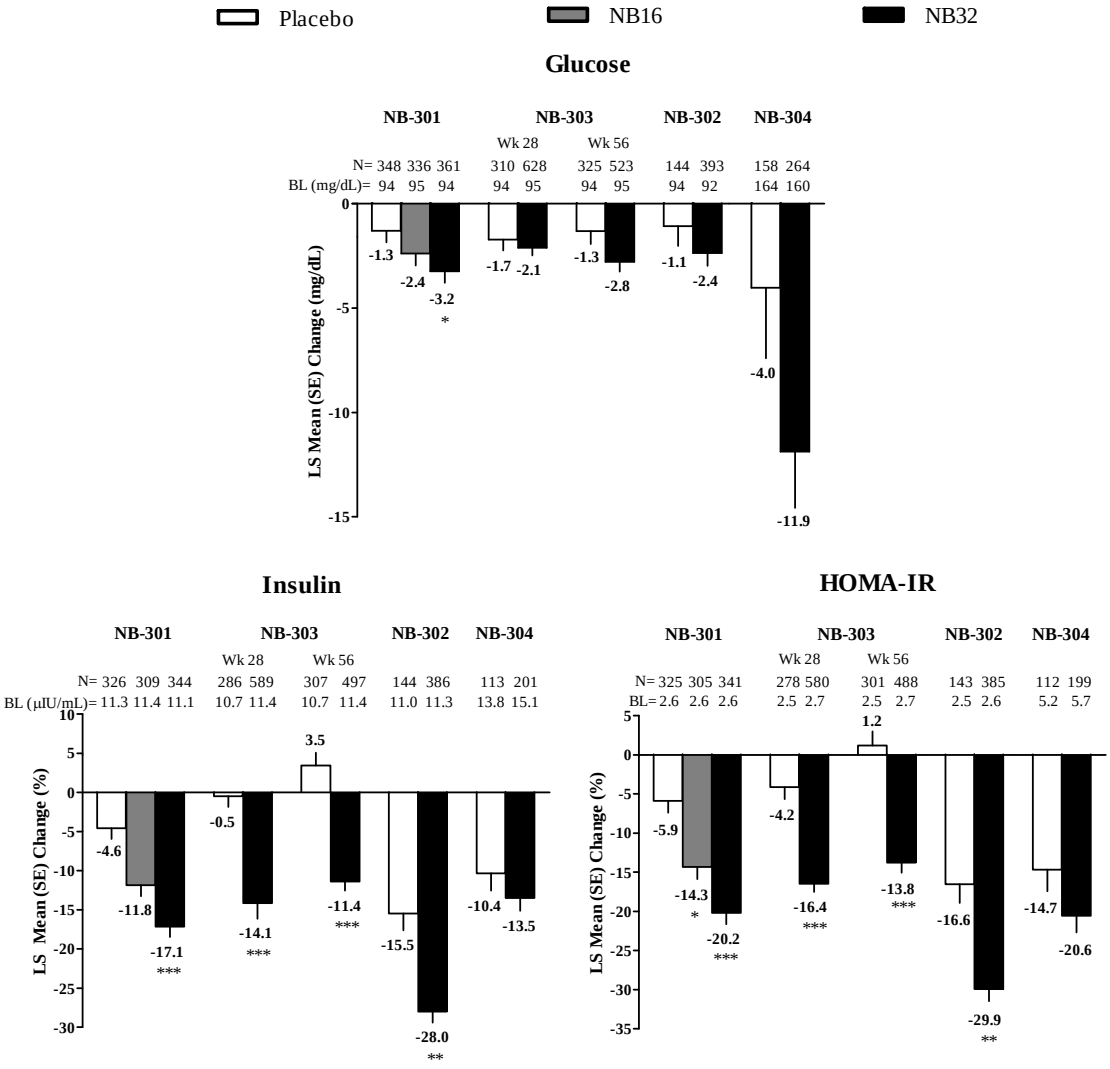
The lack of statistically significant differences in these measures may be attributed to the greater variability of fasting glucose, fasting insulin, and HOMA-IR results, as they are more impacted by the degree of compliance with fasting instructions or type of meals ingested in the day preceding the measurement than HbA1c. Furthermore, adjustments in antidiabetic medications may have influenced these results. When the use of antidiabetic medication was factored in by performing analyses that carry forward the last value prior to the medication change, the treatment effect for fasting glucose and HOM-IR was more pronounced as evidenced by the greater numerical treatment difference and nominal p values <0.05.

6.9.2.2 Glycemic Control in Nondiabetic Patients

As expected in obese and overweight patients losing clinically meaningful amounts of weight, in the three Phase 3 studies in patients without diabetes, improvements were observed in fasting glucose, fasting insulin and HOMA-IR for NB-treated patients compared with placebo-treated patients.

- At baseline, fasting glucose values ranged from 92 to 95 mg/dL across studies and were balanced between treatment groups. Treatment with NB32 (and NB16 in NB-301) across the Phase 3 studies in non-diabetic patients resulted in small decreases from baseline in glucose levels compared with placebo (Figure 21). Week 56 LS mean differences in NB32 from placebo were -1.9 mg/dL in NB-301, -1.5 mg/dL in NB-303, and -1.3 mg/dL in NB-302.
- At baseline, insulin values ranged from 10.7 to 11.4 µIU/mL across studies and were balanced between treatment groups. Treatment with NB32 (and NB16 in NB-301) across the Phase 3 studies in non-diabetic patients resulted in consistently greater percent reductions from baseline in insulin compared with placebo (Figure 21). Week 56 LS mean differences in NB32 from placebo were -12.6% in NB-301, -14.8% in NB-303, and -12.5% in NB-302.
- At baseline, HOMA-IR values ranged from 2.5 to 2.7 across studies and were balanced between treatment groups. Treatment with NB32 (and NB16 in NB-301) across the Phase 3 studies in non-diabetic patients resulted in consistently greater percent reductions from baseline in HOMA-IR compared with placebo (Figure 21). Week 56 LS mean differences in NB32 from placebo were -14.3% in NB-301, -15.0% in NB-303, and -13.4% in NB-302.

Figure 21 Glycemic Control, Change from Baseline to Endpoint by Phase 3 Study (mITT-LOCF)



Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis. For insulin and HOMA-IR, analysis used log-transformed data and baseline values are geometric means.

Abbreviations: BL= mean baseline unless specified otherwise; LS mean=least squares mean; SE=standard error.

***p<0.001, **p<0.01, *p<0.05 vs. placebo

6.9.3 Quality of Life

In addition to improvements in cardiometabolic measures that correlate with reduction in body weight, improved health-related quality of life (HRQoL) represents an important aspect of obesity therapy. QOL can be severely affected by obesity, therefore, the patient's perspective allows evaluation of the impact of disease on mood, perceived health, and self-concept. The effect of obesity on HRQoL domains may be one of the primary reasons that patients seek treatment, and HRQoL gains are often reported as the most important benefit of weight loss (Kral et al., 1992). The IWQOL-Lite, a 31-item self-report questionnaire with

questions organized into five subscales (physical function, self-esteem, sexual life, public distress, and work), was included in the four pivotal studies because it represents a valid and reliable method to detect HRQoL changes as a result of weight-loss interventions, and is the most commonly used instrument in interventional studies for obesity (Kolotkin et al., 2009). All questionnaire items were rated by patients using a 5-point scale and the total score and the subscale scores were transformed into a 0 (worst) to 100 (best) scale.

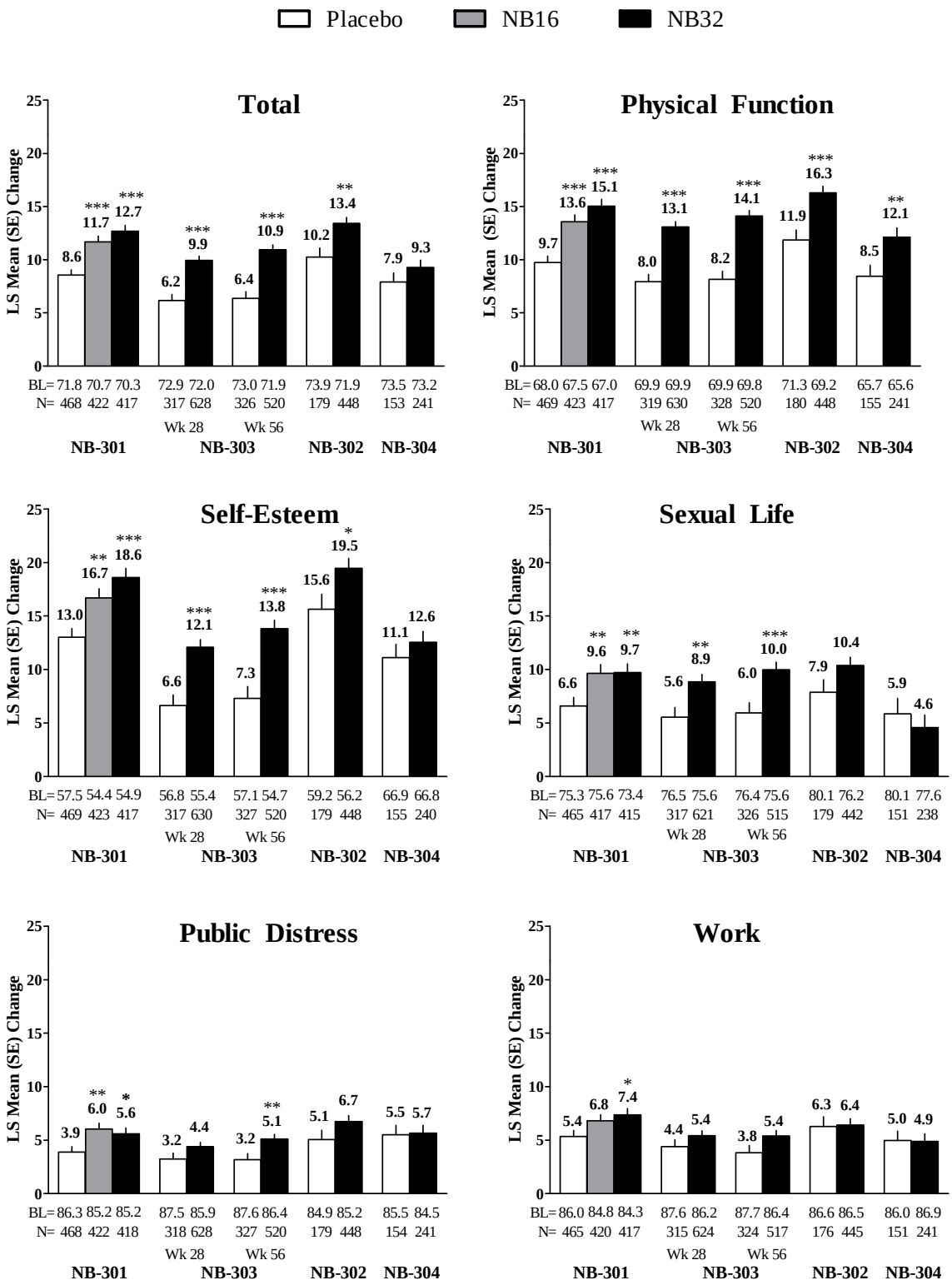
Across the four pivotal studies, at baseline, the IWQOL-Lite total score ranged from 70 to 73 in NB32-treated patients and from 72 to 74 in placebo-treated patients; these scores are indicative, on average, of moderate to severe impairment in quality of life (Crosby et al., 2004). Consistent with the scientific literature (Kolotkin et al., 2001), weight loss with NB was associated with significant improvement in the IWQOL-Lite total score compared with placebo treatment in Studies NB-301, NB-302, and NB-303 (Figure 22).

With regard to the IWQOL-Lite subscales across all four pivotal studies, at baseline the greatest degree of impairment was observed in the physical function and self-esteem subscale. At endpoint, there were improvements ($p<0.05$) in NB-treated patients (i.e., NB16 or NB32) compared with placebo-treated patients in the following subscales (Figure 22):

- Physical function (all four Phase 3 studies);
- Self-esteem (Studies NB-301, NB-302, and NB-303);
- Sexual life (Studies NB-301 and NB-303);
- Public distress (Studies NB-301 and NB-303); and
- Work (Study NB-301).

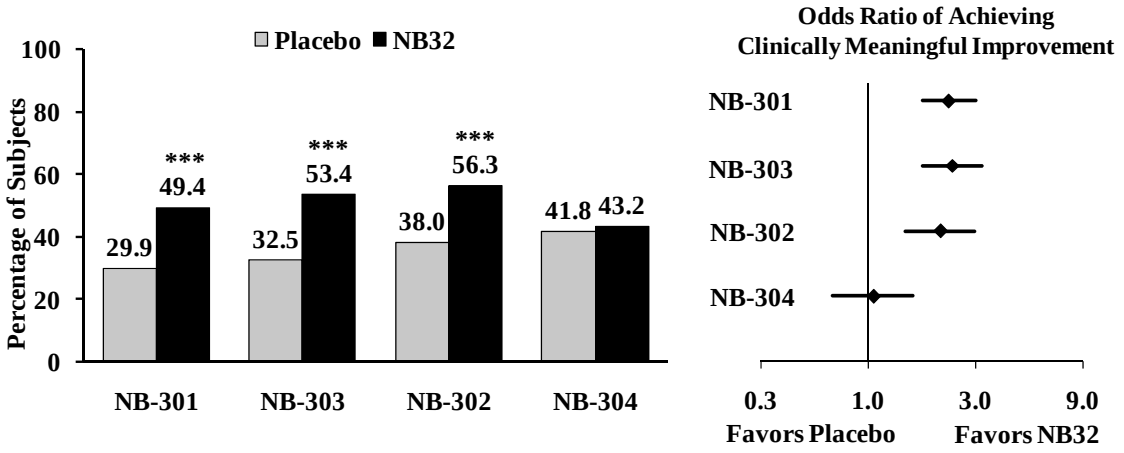
In light of the treatment effects observed in the change from baseline in IWQOL-Lite total score across the pivotal Phase 3 trials, as well as the positive treatment effects observed in IWQOL-Lite subscale scores, further analyses were conducted to determine the clinical significance of these treatment effects using an integrated methodology outlined by Crosby and colleagues (2004). This methodology integrates information from both distribution-based and anchor-based methods to establish "meaningful changes" in HRQoL for the IWQOL-Lite total score. Clinically meaningful improvements in total score were calculated based on level of baseline impairment. The range of clinically meaningful improvements is an increase from baseline in total score of 7.7 points for a patient with no baseline impairment in HRQoL to 12 points for a patient with severe impairment in HRQoL at baseline (Crosby et al., 2004). The percentage of patients achieving clinically meaningful improvements in their IWQOL-Lite total score was greater for NB32 compared with placebo treatment in Studies NB-301, NB-302, and NB-303. In studies, NB32-treated patients were more than twice as likely to achieve a clinically meaningful improvement in their IWQOL-Lite total score relative to placebo-treated patients ($p<0.001$) providing further evidence of the clinical benefits that can be derived by obese patients treated with NB32 (Figure 23).

Figure 22 IWQOL-Lite Total and Subscale Scores, Change from Baseline to Endpoint by Phase 3 Study (mITT-LOCF)



Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis.
***p<0.001, **p<0.01, *p<0.05 vs. placebo

Figure 23 IWQOL-Lite Total Score, Proportion of Patients and Odds Ratio of Achieving Clinically Meaningful Improvement from Baseline to Week 56 Endpoint by Phase 3 Study (mITT-LOCF)



NB-301 patients randomized to NB16 were included in the anchor-based improvement cutoffs, but excluded from the analysis; Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis; Data for right panel are odds ratios and associated 95% CI.

Abbreviations: CI=confidence interval.

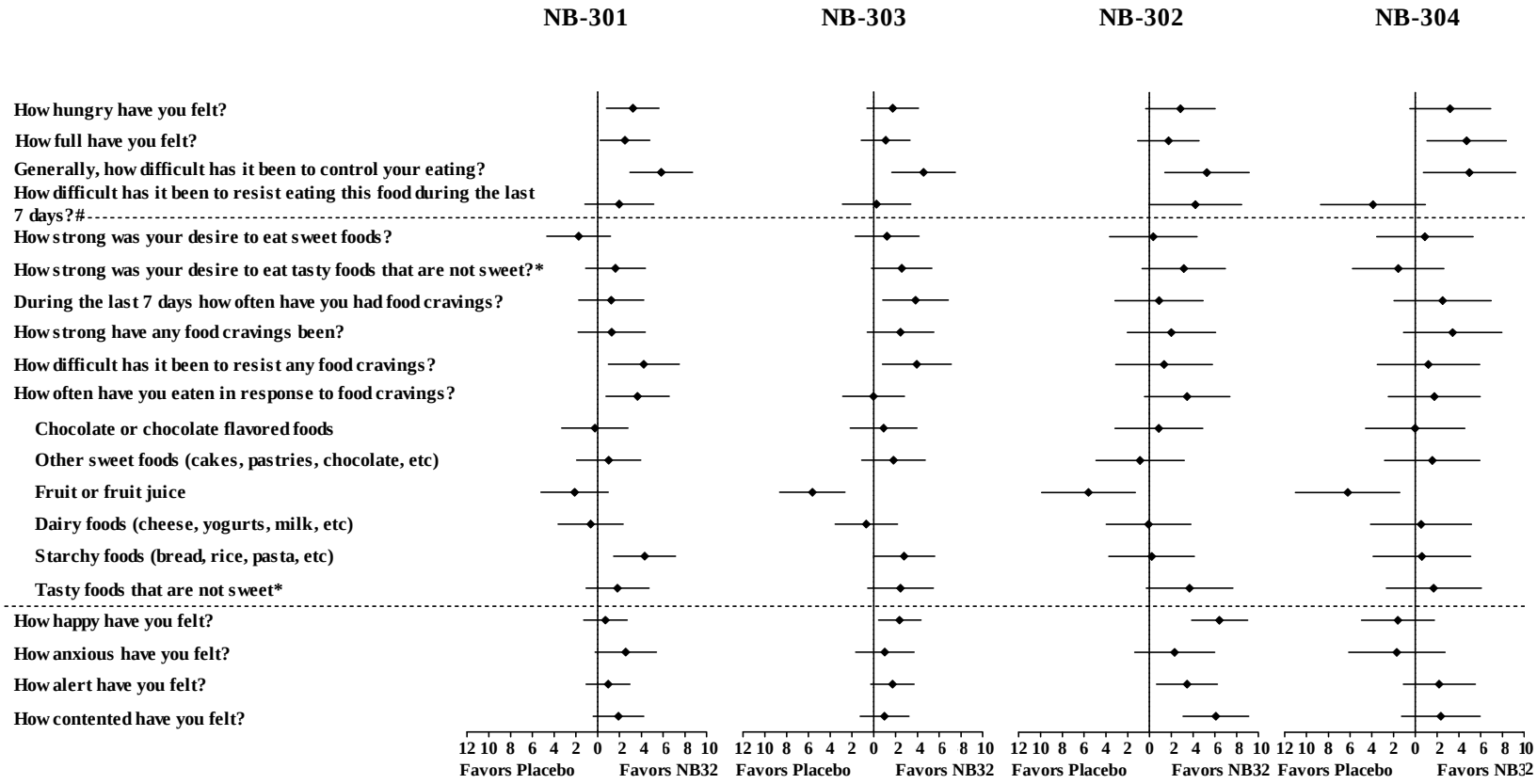
***p<0.001 vs. placebo. P-values are based on odds ratios.

6.9.4 Control of Eating

The Control of Eating (COE; Figure 24) questionnaire is composed of 20 self-report visual analog scales that explore subjective experiences that can influence food consumption. The COE exploratory questionnaire has not been fully validated, and was utilized in all four Phase 3 trials to explore the subjective patient experience during NB treatment. These include but are not limited to appetite, satiety, food cravings (in general and for specific items), and mood. Item 19 represents a summary measure of patient perception of eating control; it was pre-specified in Studies NB-301, NB-303 and NB-304 based on findings from Study NB-302.

Greater effects of NB treatment were observed in multiple items across the four pivotal studies (Figure 24). The most consistent effects were observed in Item 19 of the COE questionnaire (Generally, how difficult has it been to control your eating?) in addition to effects on other items related to decreasing hunger, increasing satiety, and increased ability to resist food cravings.

Figure 24 Control of Eating, Placebo-Corrected Change from Baseline to Week 56 Endpoint by Phase 3 Study (mITT-LOCF)



Study NB-303 Week 56 endpoint results are based upon the weighted LOCF analysis; For parameters where a negative treatment difference indicates improvement over placebo, the values are reversed so that the direction that favors NB32 remains constant; A food craving is a strong urge to eat a particular food or drink.
Patients were asked "which one food makes it most difficult for you to control eating?" prior to answering this question.
* such as french fries, potato chips, hamburgers, pizza, etc.

In addition to the COE, the Food Craving Inventory, a self-reported measure of craving for specific types of food, was also used. Unlike the findings related to control of eating, the FCI results did not evidence meaningful differences between treatment groups on food-specific craving.

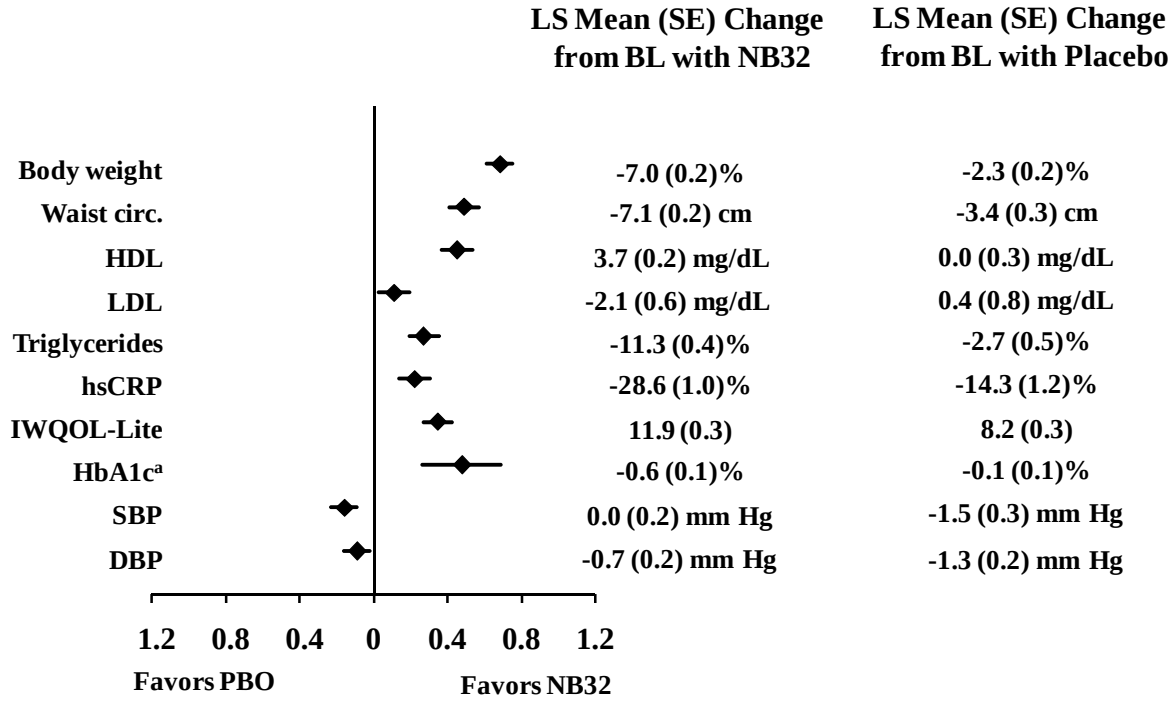
6.10 Summary of Efficacy

Four pivotal Phase 3 studies evaluated the efficacy of the recommended NB doses (NB16 and NB32) in either uncomplicated or complicated obesity. Across the Phase 3 program, treatment with NB, in conjunction with diet and exercise, resulted in early, sustained and significant weight loss as measured by the co-primary endpoints of percent change in body weight and the proportion of patients who achieved a ≥5% weight loss from baseline. The greatest change from baseline in total body weight was observed when NB32 was administered in conjunction with intense lifestyle modification. In each of the four pivotal studies, those patients who completed 56 weeks of treatment experienced greater weight loss compared with placebo treatment. Weight loss achieved with NB was primarily the result of adipose tissue loss. Significant weight loss was also observed following treatment with NB16. Finally, the efficacy of NB was observed across all demographic and clinical subgroups evaluated, including patients with hypertension, dyslipidemia, history of cardiovascular disease, type 2 diabetes, impaired fasting glucose or history of depression.

Weight loss with NB treatment resulted in clinically meaningful improvement on a number of secondary endpoints, including weight-related cardiometabolic parameters (e.g., waist circumference, triglycerides, HDL, hs-CRP). In patients with type 2 diabetes, NB treatment resulted in improved glycemic control. The small increases in mean blood pressure observed with NB were partly offset by weight loss: NB patients who experienced ≥5% and <10% weight loss demonstrated small decreases from baseline in mean blood pressure (7.6.1.1.3); greater reductions from baseline blood pressure were observed with higher levels of weight loss. Finally, favorable effects of NB treatment were observed in patient-reported outcomes, including quality of life and control of eating.

The comparisons of pooled data (NB32 and placebo) across the four pivotal studies are depicted graphically in Figure 25.

Figure 25 Effect Sizes from Baseline to Week 56 Endpoint for Primary and Secondary Endpoints in the Pooled Phase 3 Studies (mITT-LOCF)



a. HbA1c is for NB-304 only.

Data are effect size and associated 95% CI; For parameters where a negative treatment difference indicates improvement over placebo, the values are reversed so that the direction that favors NB32 remains constant.

Abbreviations: CI=confidence interval; circ=circumference; DBP= diastolic blood pressure; HDL=high-density lipoproteins; LDL=low-density lipoproteins; SBP=systolic blood pressure: SE=standard error.

7 SAFETY

7.1 Introduction

7.1.1 Safety Profiles of Naltrexone and Bupropion

Each individual constituent of the NB combination has been approved and marketed for >20 years, and both compounds have continued to undergo active clinical investigation and regulatory review, including recent approval of new indications and formulations (Table 2). Since initial approval, the number of U.S. patients exposed to naltrexone and bupropion is estimated to be approximately 1 million and 50 million, respectively.[3]

A brief review of the safety and tolerability profile of each individual agent is appropriate in the context of evaluating the NB combination. Package inserts for naltrexone and bupropion are included in Appendix 1.

Naltrexone is a potent and selective opioid antagonist that is generally regarded as a safe and well tolerated medication and is used predominantly for the treatment of alcohol dependence, with an additional indication for the treatment of opioid dependence. The most common side effects are gastrointestinal (e.g., nausea, vomiting, abdominal pain). Other AEs reported with lower frequency include headache, dizziness, nervousness/anxiety, and insomnia. While naltrexone doses of 300 mg/day have been linked with elevations in serum transaminases, the currently indicated dose of 50 mg/day is not considered to be hepatotoxic, and no cases of hepatic failure due to oral naltrexone have been identified.

Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of serotonin. Bupropion produces central nervous system stimulation of mood, attention and energy level. Adverse events commonly encountered in patients treated with bupropion include insomnia, agitation, tremor, dry mouth, dizziness and nausea. These effects are generally not severe and usually do not require discontinuation of therapy.

Bupropion produces a dose-dependent lowering of the seizure threshold and has been associated with the occurrence of seizures in a small percentage of patients. At doses up to 300 mg/day, which includes the indication for smoking cessation, the seizure incidence is approximately 0.1% (Dunner et al., 1998). Doses up to 450 mg/day of bupropion IR have a reported seizure incidence of 0.4% (Johnston et al., 1991). The risk of seizure with bupropion is generally managed through patient selection, avoiding doses above the equivalent of 450 mg bupropion IR, and gradual dose escalation. Naltrexone is not considered to impact seizure thresholds and the NB clinical program demonstrated a seizure incidence similar to the lower end of the bupropion dosing spectrum (Section 7.6.5).

All antidepressants carry class labeling for risk of suicide and suicidal behavior. This risk is predominantly established in pediatric, adolescent and young adult (≤ 24 years) patients with depression. There does not appear to be an impact of antidepressants on suicidality among

[3] Estimates Based on Wolters Kluwer Rx and Patient Data, Jan – Dec 2009 and IMS Health Rx and Persistence Data, Jan 1985 – Dec 2009.

older adults and elderly patients with depression. The NB clinical program conducted a specific review for depression and suicidality, showing no impact of NB on risk of suicide and suicidal behavior (Sections 7.6.3.1.2 and 7.6.3.1.3).

Bupropion has a well characterized, pressor effect that results in increases from placebo in blood pressure (~1-3 mm Hg) and heart rate (~1-3 bpm). Naltrexone is not known to have clinically meaningful hemodynamic effects. As described below, Study NB-201 allowed examination of blood pressure and heart rate in bupropion and naltrexone monotherapy groups compared to the NB combination. Based on NB-201 and examination across the entire phase 3 program, the impact of the NB combination on blood pressure and heart rate appears to be similar to or less than that of bupropion monotherapy, with no contribution from naltrexone. The hemodynamic effect of NB is described in Section 7.6.1.1, and an overview of bupropion's hemodynamic and cardiovascular safety is provided in Section 7.6.1.1.

7.1.2 Bupropion and Naltrexone Monotherapy in the NB Clinical Development Program

In the 24-week Phase 2 Study NB-201, bupropion or naltrexone monotherapy were compared to combination (NB) therapy. The safety findings with each of the monotherapies were consistent with the known safety profiles of the approved product labeling for each of these products. The most commonly reported AEs in Study NB-201 are summarized in Table 10. Nervous system disorders and Gastrointestinal disorders had the highest incidences of AEs. Nausea, headache, and dizziness were the AEs most commonly considered related to study treatment by the investigator and most commonly leading to discontinuation.

Only nausea and, to a lesser extent, vomiting appeared to increase in the combination treatment groups relative to bupropion or naltrexone monotherapy. Nausea appeared to be dose-related and was generally seen early, occurring within 1 to 2 weeks of the start of NB treatment. Based on the tolerability findings from this study, the initial dose-escalation period was adjusted for the Phase 3 studies (see Section 6.4 for a detailed discussion of dose selection).

Table 10 Most Common (>5%) Treatment-emergent Adverse Events in Study NB-201: Primary Treatment Period, Safety Population

MedDRA SOC Preferred Term	Placebo (N=85) n (%)	Naltrexone 48 mg (N=56) n (%)	Bupropion SR 400mg (N=60) n (%)	NB16 (N=64) n (%)	NB32 (N=63) n (%)	NB48 (N=61) n (%)
Patients with any TEAE	**59 (69.4%)**	**32 (62.5%)**	**43 (71.7%)**	**53 (82.8%)**	**50 (79.4%)**	**42 (68.9%)**
Gastrointestinal disorders	12 (14.1%)	18 (32.1%)	13 (21.7%)	30 (46.9%)	35 (55.6%)	30 (49.2%)
Abdominal pain upper	0	4 (7.1%)	0	2 (3.1%)	0	1 (1.6%)
Constipation	2 (2.4%)	0	1 (1.7%)	5 (7.8%)	10 (15.9%)	3 (4.9%)
Dry Mouth	1 (1.2%)	0	3 (5.0%)	5 (7.8%)	4 (6.3%)	4 (6.6%)
Nausea	6 (7.1%)	12 (21.4%)	5 (8.3%)	20 (31.3%)	27 (42.9%)	27 (44.3%)
Vomiting	1 (1.2%)	3 (5.4%)	3 (5.0%)	5 (7.8%)	7 (11.1%)	7 (11.5%)
Infections and infestations	28 (32.9%)	13 (23.2%)	17 (28.3%)	15 (23.4%)	22 (34.9%)	13 (21.3%)
Influenza	1 (1.2%)	3 (5.4%)	3 (5.0%)	0	6 (9.5%)	1 (1.6%)
Nasopharyngitis	15 (17.6%)	5 (8.9%)	3 (5.0%)	4 (6.3%)	5 (7.9%)	2 (3.3%)
Sinusitis	5 (5.9%)	1 (1.8%)	5 (8.3%)	5 (7.8%)	3 (4.8%)	3 (4.9%)
Musculoskeletal and connective tissue disorders	9 (10.6%)	1 (1.8%)	2 (3.3%)	4 (6.3%)	4 (6.3%)	7 (11.5%)
Back pain	2 (2.4%)	0	0	0	0	5 (8.2%)
Nervous system disorders	18 (21.2%)	13 (23.2%)	13 (21.7%)	19 (29.7%)	16 (25.4%)	19 (31.1%)
Dizziness	0	5 (8.9%)	6 (10.0%)	8 (12.5%)	6 (9.5%)	7 (11.5%)
Headache	11 (12.9%)	5 (8.9%)	4 (6.7%)	7 (10.9%)	9 (14.3%)	9 (14.8%)
Psychiatric disorders	14 (16.5%)	9 (16.1%)	10 (16.7%)	11 (17.2%)	9 (14.3%)	7 (11.5%)
Anxiety	1 (1.2%)	2 (3.6%)	3 (5.0%)	4 (6.3%)	3 (4.8%)	3 (4.9%)
Insomnia	7 (8.2%)	5 (8.9%)	7 (11.7%)	5 (7.8%)	5 (7.9%)	1 (1.6%)
Vascular disorders	1 (1.2%)	5 (8.9%)	1 (1.7%)	3 (4.7%)	1 (1.6%)	2 (3.3%)
Hypertension	1 (1.2%)	3 (5.4%)	1 (1.7%)	0	0	2 (3.3%)

Note: Most common defined as >5% incidence of specific event in any treatment group.
Abbreviations: SOC=system organ class. For Study NB-201, NB16=naltrexone 16mg/bupropion 400 mg, NB32=naltrexone 32mg/bupropion 400 mg, NB48=naltrexone 48mg/bupropion 400 mg.

The vital signs data from Study NB-201 showed mean changes in blood pressure and heart rate that were small across all groups. The bupropion monotherapy arm appeared to have a greater incidence of elevations in systolic (SBP) and diastolic blood pressure (DBP) and heart rate that is consistent with the literature on bupropion effects. Compared to bupropion monotherapy, the NB groups appeared to demonstrate similar or smaller changes from baseline in these measures. Additionally, there was no evidence from Study NB-201 that naltrexone substantially affected blood pressure or heart rate.

There were no meaningful adverse effects associated with bupropion or naltrexone monotherapy or NB combination treatment on measures of anxiety or depression, laboratory evaluations, or electrocardiographic measurements in this 24-week study.

Table 11 Mean Changes from Baseline at Week 24 in Vital Signs in Study NB-201: Primary Treatment Period, Safety Population

	Placebo (N=85)		Naltrexone 48 mg (N=56)		Bupropion SR 400mg (N=60)		NB16 (N=64)		NB32 (N=63)		NB48 (N=61)	
	N	**mean±SD**	**N**	**mean±SD**	**N**	**mean±SD**	**N**	**mean±SD**	**N**	**mean±SD**	**N**	**mean±SD**
Systolic Blood Pressure (mm Hg)												
Baseline	85	119.29±10.51	56	118.45±9.45	60	115.70±11.11	64	117.67±10.77	63	118.13±10.40	61	116.23±11.17
Mean Change at Wk 24	64	-1.98±11.57	34	1.24±10.57	44	2.33±11.85	40	0.90±12.27	49	-3.04±12.29	33	4.00±9.40
Diastolic Blood Pressure (mm Hg)												
Baseline	85	76.36±7.17	56	75.75±7.69	60	74.30±7.42	64	75.34±7.67	63	72.79±7.78	61	75.07±7.52
Mean Change at Wk 24	64	-4.83±10.33	34	-0.47±6.77	44	-0.27±8.41	40	-1.10±8.10	49	-0.67±8.17	33	-1.18±5.71
Heart Rate (bpm)												
Baseline	85	69.82±7.58	56	68.04±6.64	60	69.53±7.78	64	67.72±6.89	63	69.62±7.00	61	69.61±9.01
Mean Change at Wk 24	64	0.02±7.70	34	-0.62±6.56	44	1.26±5.83	40	3.75±8.24	49	0.69±5.92	33	-0.77±8.79

Abbreviations: SD=standard deviation. For Study NB-201, NB16=naltrexone 16mg/bupropion 400 mg, NB32=naltrexone 32mg/bupropion 400 mg, NB48=naltrexone 48mg/bupropion 400 mg.

7.1.3 Integrated Safety Evaluation of NB

The safety and tolerability of NB was evaluated in the 23 studies comprising the NB clinical development program, including 15 Phase 1, four Phase 2, and four Phase 3 investigations. A total of 3475 patients have been exposed to NB in Phase 2 and 3 studies for a total of 2313 patient-years.

The overall assessment of the safety of NB was based on evaluation of the safety data for each individual study and evaluation of the pooled safety data, which included Study NB-201 and the Phase 3 studies. The focus of the safety discussion in this briefing document will be on the randomized, placebo-controlled, double-blind, pooled data (Primary Dataset; Table 12), with the exceptions of comparisons of patients with type 2 diabetes using Study NB-304 (Diabetic Dataset) to patients without diabetes (Nondiabetic Dataset) and evaluations of dose relatedness of AEs using Study NB-301 and the Nondiabetic Dataset. All eight Phase 2 and 3 studies are integrated for the exposure data.

Table 12 Datasets for Safety Analyses

Study	Phase	Primary Dataset	Nondiabetic Dataset	Diabetic Dataset
NB-201	2	X	X	
NB-301	3	X	X	
NB-302	3	X	X	
NB-303	3	X	X	
NB-304	3	X		X

The Primary Dataset includes safety data from 3239 patients treated with NB and 1515 patients treated with placebo from five placebo-controlled, long-term Phase 2 and 3 studies as described in Table 13. When applicable, data from all NB doses are pooled together to form one NB treatment group.

Table 13 NB Clinical Development Program – Primary Safety Analysis Dataset

Safety Analysis Dataset	Studies Included*	Total Number of Patients
Primary	NB-201 (excluding 24-week extension phase) NB-301 (excluding 2-week discontinuation phase) NB-303 NB-302 NB-304	Placebo: 1515 NB16: 633 NB32: 2545 NB: 3239**

* NB-201 includes a 24-week double-blind treatment phase; all others are 56 weeks in duration.
** Includes 61 patients treated with NB48 in Study NB-201. Given the similar tolerability relative to patients treated with NB32, data from this dose group are not shown separately.

Throughout the discussion of safety in this briefing document, data for the Total NB and NB32 groups relative to placebo are generally presented in the summaries of data; however, in certain instances only the Total NB group is presented due to small numbers of patients (e.g., subgroup analyses, SAEs).

In the following sections of this briefing document, safety data from the Phase 3 studies and NB-201 (Primary Dataset) will be presented and support the following observations:

- Overview of AEs: The majority of events occurred early in treatment, were mild to moderate in severity, and most resolved without treatment discontinuation. Serious AEs were infrequent and occurred at a similar incidence in both the NB and placebo groups.

- AEs in type 2 diabetes and other subpopulations: The frequency and severity of AEs reported by obese/overweight patients with type 2 diabetes was generally similar to those reported by patients without diabetes, with the exception of increased nausea, vomiting, diarrhea, and hypertension AEs relative to placebo. Relative to placebo, changes in blood pressure in patients with diabetes were generally similar to or less than that observed in patients without diabetes. No clinically meaningful differences were observed in other subpopulations (e.g., age, ethnicity, race, sex, baseline smoking status, baseline antihypertensive medication, by ≥5% weight loss at endpoint, and obesity class).

- Events of clinical interest specific to naltrexone and bupropion: Effects of NB were consistent with the established safety profile for each of the components. There were no qualitatively different types of AEs.

    - There was no evidence of increased depression or suicidality.

    - Rate of seizures was consistent with the historical rates observed in studies with lower-dose bupropion SR (300 mg).

    - NB treatment was associated with increases of approximately 1 mm Hg in mean SBP and DBP early (at weeks 4 and 8) in treatment. By week 12, mean blood pressure returned to baseline with subsequent reductions below baseline of approximately 1 mm Hg. Weight loss is generally associated with decreases in mean blood pressure; this effect was observed for both NB and placebo patients.

    - The majority of both NB- and placebo-treated patients with outlier increases in SBP, DBP, or heart rate occurred early in treatment; the proportion of patients with outlier values was generally greater in the Total NB group compared with the placebo group.

    - Cardiovascular AEs were generally balanced between the two treatment groups. Major cardiovascular events (based on Custom MACE analysis) were low in frequency, with 1 event in placebo (<0.1%) and 3 events in Total NB (<0.1%). While the results do not suggest a specific trend in the data, the limited number of events precludes definitive conclusions regarding the potential impact of NB on ischemic cardiovascular events.

- Other: There were no clinically meaningful changes in physical examination findings, laboratory findings, ECG results, or other safety measures.

7.2 Extent of Exposure

In all pooled Phase 2 and 3 studies, there were more than twice as many patients exposed to NB (N=3475) in the pooled dose groups of NB16, NB32, or NB48/50 compared with patients exposed to placebo (N=1533), primarily due to a 1:2 or 1:3 randomization of placebo to NB treated patients in the Phase 3 studies. Overall, 1661 patients received ≥52 weeks of NB treatment, of which, 1589 patients had exposures of ≥56 weeks (reflecting at least 52 weeks of exposure at the maintenance dose). The mean exposure, in weeks, was generally similar across dose and treatment groups. A total of 1092 patient-years of exposure was obtained for placebo patients and 2313 patient-years of exposure for NB-treated patients (Table 14). Duration of exposure was considerably lower in the NB48/50 group compared with other groups due to a shorter study duration for Studies OT-101 and NB-201, which are the only studies with initial randomization to these doses.

Table 14 Summary of Exposure by Weeks: All Pooled Phase 2 and 3 Studies

Duration of Exposure	Placebo (N=1533)	NB16 (N=635)	NB32 (N=2695)	NB48/50 (N=269)	Total NB (N=3475)
Weeks, Mean (SD)	37.59 (21.77)	34.81 (24.38)	35.01 (23.18)	21.40 (12.98)	35.16 (23.64)
≥6 months, n	937	374	1617	115	2033
≥12 months, n	788	287	1270	0	1661
Patient-years	1092	418	1786	109	2313

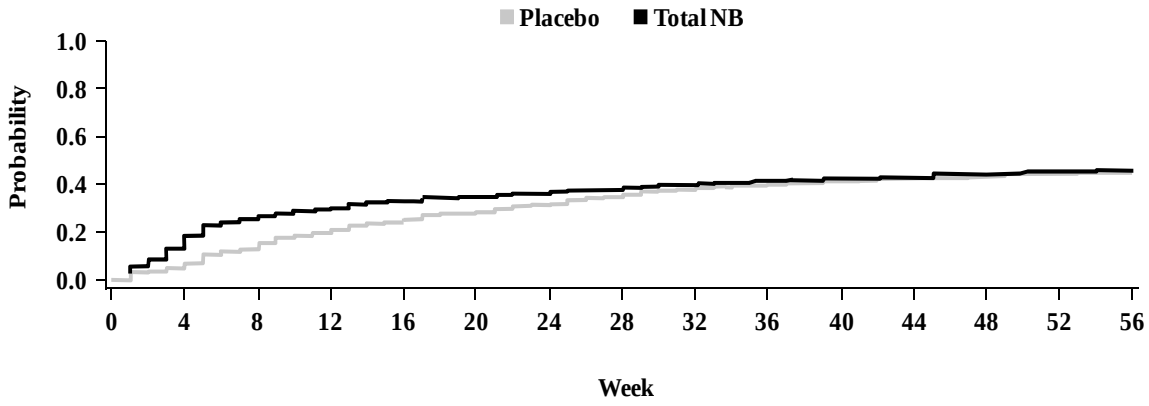
Patient-years is defined as the sum of days of exposure for all patients divided by 365.25 days.
Abbreviations: SD=standard deviation; Total NB=all doses of combination naltrexone and bupropion treatment.

Similarly, in the Primary Dataset twice as many patients were exposed to NB (N=3239) compared with patients exposed to placebo (N=1515). The four Phase 3 studies provided for up to 56 weeks of exposure to NB or placebo, while the placebo-controlled period in Study NB-201 provided up to 24 weeks of exposure.

7.3 Patient Disposition

In the Primary Dataset, a similar percentage of patients completed treatment across the Total NB and placebo groups (Table 15). The most common reasons for discontinuation of treatment were AEs, lost to follow-up, and withdrawal of consent. The incidence of discontinuation due to AEs was higher (22.9% vs. 12.0%) in the Total NB group compared with the placebo group, while the incidence of withdrawal of consent (8.6% vs. 12.7%) and withdrawal due to insufficient weight loss (1.7% vs. 6.1%) was lower in the Total NB group compared with the placebo group. The largest percentage of dropouts in the Total NB group per study visit occurred during the dose-escalation phase (Figure 26); thereafter, the percentage of patients discontinuing was similar from visit to visit.

Figure 26 Overall Discontinuations by Week: Primary Dataset, Double-Blind Treatment Phase



Event probabilities are based on the Kaplan-Meier method. Stratified logrank test is stratified by study.
Abbreviations: NB=all doses of combination naltrexone and bupropion treatment.

The proportion of total discontinuations observed in both the placebo and NB groups was anticipated based upon findings from earlier studies performed with other agents in obesity clinical trials (Padwal and Majumdar, 2007). This anticipated discontinuation rate was factored into power calculations for determining the number of patients required for studies in the NB Phase 3 program.

Table 15 Summary of Disposition: Primary Dataset

Primary Dataset	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Completed Treatment	828 (54.7%)	322 (50.9%)	1401 (55.0%)	1747 (53.9%)
Discontinued Treatment	687 (45.3%)	311 (49.1%)	1144 (45.0%)	1492 (46.1%)
Reason for discontinuing treatment:				
Adverse event	182 (12.0%)	129 (20.4%)	604 (23.7%)	742 (22.9%)
Withdrew consent	192 (12.7%)	67 (10.6%)	202 (7.9%)	278 (8.6%)
Lost to follow-up	145 (9.6%)	77 (12.2%)	166 (6.5%)	258 (8.0%)
Insufficient weight loss	92 (6.1%)	14 (2.2%)	40 (1.6%)	54 (1.7%)
Other[a]	76 (5.0%)	24 (3.8%)	132 (5.2%)	160 (4.9%)

a. Other includes: drug non-compliance, enrolled but did not meet selection criteria, failure to comply with protocol requirements, patient became pregnant, patient moved, randomized but study drug not dispensed, other primary reason not listed, and death.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Patient disposition in the Diabetic and Nondiabetic Datasets was generally consistent with the Primary Dataset. In the Diabetic Dataset, discontinuation due to an AE was more frequent than in the Nondiabetic Dataset (29.4% vs. 22.9%, respectively, in the NB32 group and 15.4% vs. 11.6%, respectively, in the placebo group).

The proportion of patients who discontinued without a termination visit (lost to follow-up, LTFU) was greater in the placebo group (9.6%) than in the pooled NB group (8.0%). Across both treatment groups, demographic characteristics of LTFU patients tended to be similar to

those of the general study population, except that they were younger on average. The proportions of AE types and severities reported by patients prior to LTFU were similar to those reported from patients who remained on study.

7.4 Adverse Events

Although AE information was captured for up to 30 days after study completion or discontinuation, AE summaries are based on treatment-emergent AEs, defined as events experienced from time of first dose to 7 days after the last confirmed dose. A post-dose window of 7 days was chosen because one week represents approximately 5 half-lives for bupropion, naltrexone, and their metabolites, and therefore allows sufficient time for significant clearance to have taken place. Treatment-emergent AEs were further defined as events that first occurred or worsened during the indicated treatment phase. Events captured post 7 days after the last confirmed dose or prior to treatment were evaluated as non-treatment-emergent and will not be generally discussed in this briefing document unless otherwise specified. Post-treatment AEs occurred in less than 3% in any group, with no individual event occurring at an incidence higher than 0.1%, and did not change the overall safety conclusions.

Data from the placebo, NB32, and Total NB groups will be presented in this briefing document for the discussion of AEs. Data from the NB16 and/or NB48 groups will only be presented in the context of dose comparison (Section 7.4.5) and to provide an overview of all AEs.

7.4.1 Overview of Adverse Events

A summary of AEs occurring during the double-blind treatment phase is provided in Table 16. More patients treated with NB experienced an AE than those treated with placebo (85.5% vs. 75.0%). The majority of AEs reported were mild to moderate in severity. A higher percentage of severe events were experienced by patients in the Total NB group than those in the placebo group (13.8% vs. 9.2%), primarily due to nausea, headache, vomiting, constipation, and dizziness. The incidence of SAEs was low but slightly higher in the Total NB group compared with the placebo group (2.7% vs. 2.2%). One sudden death, resulting from a presumed myocardial infarction, occurred in a 65-year-old man with multiple cardiac risk factors and was considered unlikely to be related to NB treatment by the investigator (details in Section 7.4.3.1). The incidence of patients discontinuing treatment due to an AE was higher in the Total NB group than in the placebo group (27.8% vs. 15.9%), with the majority due to intolerability of the study medication experienced early after treatment initiation, as discussed in Section 7.4.4.

Table 16 Overview of 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 (%)	
Patients with AEs								
Any AE/Severity[a]	1137	(75.0%)	507	(80.1%)	2221	(87.3%)	2769	(85.5%)
Mild	479	(42.1%)	217	(42.8%)	800	(36.0%)	1040	(37.6%)
Moderate	553	(48.6%)	232	(45.8%)	1100	(49.5%)	1347	(48.6%)
Severe	105	(9.2%)	58	(11.4%)	321	(14.5%)	382	(13.8%)
Patients with SAEs								
Any treatment-emergent SAE[b]	25	(1.7%)	10	(1.6%)	64	(2.5%)	74	(2.3%)
Deaths	0		0		1	(<0.1%)	1	(<0.1%)
Patients discontinuing treatment due to any AE								
Any AE	181	(11.9%)	139	(22.0%)	612	(24.0%)	771	(23.8%)

a. Maximum severity of events is shown, and percentages are based on the number of patients with any AE. Percentages elsewhere in the table are based on the number of patients.
b. Includes the one death noted elsewhere in this table.

Abbreviations: AE=adverse event; SAE=serious adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

7.4.2 Common Adverse Events

The AE categories reported at the highest incidence were Gastrointestinal Disorders, Nervous System Disorders, and Infections and Infestations (Table 17). Adverse events that occurred in at least 1% of patients and more frequently in NB-treated patients over placebo-treated patients are summarized in Table 18. The most common AEs (those that occurred at a ≥5% incidence in the Total NB group and greater than the incidence in the placebo group) for the Total NB group (all doses combined) were nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea. These common AEs are consistent with the AE profiles described in the prescribing information for approved bupropion- and naltrexone-containing products.

Generally, the most common events occurred early in treatment (i.e., during the dose-escalation phase) in the Total NB group (Table 19) and typically resolved without the need for additional interventions while continuing NB treatment.

Table 17 Common System Organ Classes (≥10% in Any Group): Primary Dataset, Double-Blind Treatment Phase

System Organ Class	Placebo (N=1515) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Patients with any AE	**1137 (75.0%)**	**2221 (87.3%)**	**2769 (85.5%)**
Gastrointestinal Disorders	409 (27.0%)	1454 (57.1%)	1794 (55.4%)
Nervous System Disorders	287 (18.9%)	901 (35.4%)	1115 (34.4%)
Infections & Infestations	570 (37.6%)	888 (34.9%)	1101 (34.0%)
Psychiatric Disorders	213 (14.1%)	517 (20.3%)	608 (18.8%)
Musculoskeletal & Connective Tissue Disorders	281 (18.5%)	395 (15.5%)	485 (15.0%)
General Disorders & Administration Site Conditions	185 (12.2%)	399 (15.7%)	481 (14.9%)
Skin & Subcutaneous Tissue Disorders	148 (9.8%)	333 (13.1%)	409 (12.6%)
Injury, Poisoning & Procedural Complications	155 (10.2%)	271 (10.6%)	334 (10.3%)
Respiratory, Thoracic & Mediastinal Disorders	202 (13.3%)	271 (10.6%)	329 (10.2%)

Abbreviations: AE= adverse event; Total NB=all doses of combination naltrexone and bupropion treatment.

Table 18 Treatment-emergent Adverse Events occurring in ≥1% of the Total NB Group and Greater than Placebo: Primary Dataset, Double-Blind Treatment Phase

MedDRA Preferred Term	Placebo (N=1515) n (%)		NB32 (N=2545) n (%)		Total NB (N=3239) n (%)	
Patients with any AE	**1137**	**(75.0%)**	**2221**	**(87.3%)**	**2769**	**(85.5%)**
Nausea	102	(6.7%)	828	(32.5%)	1030	(31.8%)
Constipation	109	(7.2%)	489	(19.2%)	587	(18.1%)
Headache	157	(10.4%)	447	(17.6%)	554	(17.1%)
Vomiting	44	(2.9%)	273	(10.7%)	321	(9.9%)
Dizziness	51	(3.4%)	252	(9.9%)	311	(9.6%)
Insomnia	89	(5.9%)	233	(9.2%)	277	(8.6%)
Dry mouth	35	(2.3%)	205	(8.1%)	256	(7.9%)
Diarrhoea	79	(5.2%)	180	(7.1%)	215	(6.6%)
Fatigue	52	(3.4%)	103	(4.0%)	130	(4.0%)
Anxiety	43	(2.8%)	108	(4.2%)	127	(3.9%)
Tremor	10	(0.7%)	103	(4.0%)	126	(3.9%)
Hot flush	18	(1.2%)	108	(4.2%)	124	(3.8%)
Tinnitus	9	(0.6%)	83	(3.3%)	110	(3.4%)
Influenza	49	(3.2%)	87	(3.4%)	108	(3.3%)
Abdominal pain upper	20	(1.3%)	88	(3.5%)	102	(3.1%)
Gastroenteritis viral	40	(2.6%)	88	(3.5%)	102	(3.1%)
Urinary tract infection	42	(2.8%)	83	(3.3%)	99	(3.1%)
Hypertension	34	(2.2%)	82	(3.2%)	94	(2.9%)
Abdominal pain	21	(1.4%)	71	(2.8%)	88	(2.7%)
Dysgeusia	10	(0.7%)	61	(2.4%)	77	(2.4%)
Hyperhidrosis	9	(0.6%)	65	(2.6%)	77	(2.4%)
Palpitations	13	(0.9%)	54	(2.1%)	77	(2.4%)
Irritability	28	(1.8%)	66	(2.6%)	74	(2.3%)
Rash	31	(2.0%)	62	(2.4%)	74	(2.3%)
Blood pressure increased	22	(1.5%)	61	(2.4%)	73	(2.3%)
Muscle strain	25	(1.7%)	55	(2.2%)	66	(2.0%)
Dyspepsia	17	(1.1%)	44	(1.7%)	56	(1.7%)
Alopecia	11	(0.7%)	46	(1.8%)	55	(1.7%)
Pruritus	13	(0.9%)	48	(1.9%)	55	(1.7%)
Vision blurred	15	(1.0%)	46	(1.8%)	52	(1.6%)
Migraine	21	(1.4%)	43	(1.7%)	51	(1.6%)
Heart rate increased	17	(1.1%)	43	(1.7%)	46	(1.4%)
Disturbance in attention	5	(0.3%)	39	(1.5%)	45	(1.4%)
Contusion	10	(0.7%)	33	(1.3%)	44	(1.4%)
Pyrexia	20	(1.3%)	35	(1.4%)	44	(1.4%)
Urticaria	18	(1.2%)	34	(1.3%)	44	(1.4%)
Pain	12	(0.8%)	39	(1.5%)	42	(1.3%)
Somnolence	12	(0.8%)	32	(1.3%)	42	(1.3%)
Feeling jittery	5	(0.3%)	36	(1.4%)	41	(1.3%)
Gastroenteritis	15	(1.0%)	27	(1.1%)	41	(1.3%)
Gastroeosophageal reflux disease	14	(0.9%)	31	(1.2%)	40	(1.2%)
Sleep disorder	12	(0.8%)	34	(1.3%)	37	(1.1%)
Vertigo	4	(0.3%)	30	(1.2%)	36	(1.1%)

Table 18 Treatment-emergent Adverse Events occurring in ≥1% of the Total NB Group and Greater than Placebo: Primary Dataset, Double-Blind Treatment Phase (*Continued*)

MedDRA Preferred Term	Placebo (N=1515) n (%)		NB32 (N=2545) n (%)		Total NB (N=3239) n (%)	
Toothache	15	(1.0%)	31	(1.2%)	35	(1.1%)
Flatulence	13	(0.9%)	29	(1.1%)	32	(1.0%)
Seasonal allergy	14	(0.9%)	27	(1.1%)	32	(1.0%)
Lethargy	4	(0.3%)	26	(1.0%)	31	(1.0%)

Abbreviations: AE=adverse event; Total NB=all doses of combination naltrexone and bupropion treatment.

Table 19 Most Common (≥5% Total NB and Greater than Placebo) Adverse Events by Treatment Phase: Primary Dataset

MedDRA Preferred Term	Placebo (N=1515) n (%)		NB32 (N=2545) n (%)		Total NB (N=3239) n (%)	
Dose-Escalation Treatment Phase (through Week 4/5)[a]						
Patients with any AE	**564**	**(37.2%)**	**1643**	**(64.6%)**	**2025**	**(62.5%)**
Nausea	61	(4.0%)	643	(25.3%)	804	(24.8%)
Headache	81	(5.3%)	291	(11.4%)	351	(10.8%)
Constipation	41	(2.7%)	290	(11.4%)	344	(10.6%)
Dizziness	21	(1.4%)	179	(7.0%)	226	(7.0%)
Dry mouth	25	(1.7%)	171	(6.7%)	216	(6.7%)
Insomnia	44	(2.9%)	161	(6.3%)	197	(6.1%)
Vomiting	13	(0.9%)	146	(5.7%)	173	(5.3%)
Maintenance Treatment Phase (post Week 4/5)[b]						
Patients with any AE	**973**	**(64.2%)**	**1585**	**(62.3%)**	**1971**	**(60.9%)**
Nausea	46	(3.0%)	261	(10.3%)	320	(9.9%)
Constipation	72	(4.8%)	223	(8.8%)	272	(8.4%)
Headache	84	(5.5%)	186	(7.3%)	241	(7.4%)
Vomiting	32	(2.1%)	145	(5.7%)	172	(5.3%)

a. *Dose-escalation phase:* AEs that occurred within 35 days of first dose date for Study NB-303 and within 28 days for the other studies.

b. *Maintenance Phase:* AEs that occurred greater than 35 days of first dose date for Study NB-303 and greater than 28 days for the other studies.

Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; Total NB=all doses of combination naltrexone and bupropion treatment.

The majority of AEs were considered to be mild to moderate in severity. Severe AEs were reported more frequently by patients in the Total NB group than those in the placebo group (11.8% vs. 6.9%; Table 20). The most common severe AEs in NB-treated patients are summarized in Table 20. The most common severe AEs with the greatest difference relative to placebo were nausea, headache, and constipation.

Table 20 Most Common Severe Treatment-Emergent Adverse Events (≥0.4% Total NB and at Least Twice the Incidence of Placebo): Primary Dataset, Double-Blind Treatment Phase

Preferred Term	Placebo (N=1515) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Severe AE	**105 (6.9%)**	**321 (12.6%)**	**382 (11.8%)**
Nausea	1 (<0.1%)	53 (2.1%)	63 (1.9%)
Headache	5 (0.3%)	28 (1.1%)	35 (1.1%)
Vomiting	5 (0.3%)	19 (0.7%)	22 (0.7%)
Constipation	2 (0.1%)	16 (0.6%)	20 (0.6%)
Dizziness	3 (0.2%)	14 (0.6%)	18 (0.6%)
Abdominal pain upper	3 (0.2%)	10 (0.4%)	14 (0.4%)
Migraine	2 (0.1%)	11 (0.4%)	12 (0.4%)
Insomnia	1 (<0.1%)	12 (0.5%)	14 (0.4%)

Abbreviations: AE=adverse event; Total NB=all doses of combination naltrexone and bupropion treatment.

Study NB-301 evaluated a sudden versus tapered dosing for discontinuation of study medication. The incidence and type of AEs during the drug discontinuation phase were similar for NB16 (7.7% for sudden and 9.2% for tapered), NB32 (8.9% sudden and 9.5% tapered), and placebo (8.5%) groups, regardless of discontinuation method.

7.4.2.1 Subgroup Analyses: Primary Dataset, Double-Blind Treatment Phase

Subgroup analyses by ethnicity, race, sex, baseline smoking status, baseline antihypertensive medication, by ≥5% weight loss at endpoint, and obesity class (BMI categories of <30, 30 to <35, 35 to <40, and ≥40) revealed no meaningful differences in AEs overall or events within a given system organ class (SOC) (Appendix 8, Table 74). Subgroup analyses by age showed no meaningful differences between patients 18 to 44 years of age or 45 to 64 years of age; however, in the small number of patients ≥65 years of age, the following trend was observed:

- In the Total NB group, a higher incidence of dizziness, tremor, and hypertension was noted in patients ≥65 years of age compared with patients 18 to 44 years of age or 45 to 64 years old. Although it would be expected that older patients would be more likely to experience these events, the small number of patients ≥65 years of age (n=62) relative to the other subgroups and the high proportion of these patients with diabetes (58%) precludes definitive conclusions (Table 21). The same pattern was observed in the NB32 treatment group. Dizziness and hypertension are discussed in greater detail in Sections 7.6.4 and 7.6.1, respectively.

Table 21 Selected Treatment-Emergent Adverse Events by Age Category: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515) n (%)			Total NB (N=3239) n (%)		
MedDRA Preferred Term	**18-44 yrs (n=686)**	**45-64 yrs (n=797)**	**≥65 yrs (n=32)**	**18-44 yrs (n=1443)**	**45-64 yrs (n=1734)**	**≥65 yrs (n=62)**
Patients with any AE	**483 (70.4)**	**629 (78.9%)**	**25 (78.1%)**	**1185 (82.1%)**	**1523 (87.8%)**	**61 (98.4%)**
Dizziness	18 (2.6%)	32 (4.0%)	1 (3.1%)	121 (8.4%)	174 (10.0%)	16 (25.8%)
Tremor	2 (0.3%)	8 (1.0%)	0	48 (3.3%)	67 (3.9%)	11 (17.7%)
Hypertension	10 (1.5%)	22 (2.8%)	2 (6.3%)	16 (1.1%)	69 (4.0%)	9 (14.5%)

Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; Total NB=all doses of combination naltrexone and bupropion treatment.

7.4.3 Deaths and Other Serious Adverse Events

7.4.3.1 Deaths

A single death was reported in the NB clinical program. A 65-year-old White male in the NB32 group, with a medical history of gout, hypercholesterolemia, hypertension, and idiopathic bradycardia with primary atrioventricular block, died suddenly on study Day 324 from an event that was presumed by the investigator to be a myocardial infarction. No autopsy was performed. Per the medical examiner narrative, the cause of death was attributed to atherosclerotic coronary artery disease. The last dose of study drug was Day 324. This event was considered to be unlikely related to study drug by the investigator and is discussed in more detail in Section 7.6.2.1 with a narrative of the event provided in Section 7.6.2.1.1.

7.4.3.2 Other Serious AEs

The incidence of SAEs in the Total NB group was low but higher compared with that observed in the placebo group (2.3% vs. 1.7%). A summary of all treatment-emergent SAEs is presented in Table 22. A total of 13 patients had a posttreatment SAE (occurred >7 days after last treatment): 11 in the NB group and 2 in the placebo group). No single posttreatment SAE was reported in more than one patient. Cholecystitis and cardiovascular SAEs are discussed in Sections 7.6.7.2 and 7.6.2.1, respectively.

Table 22 Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (includes SOC categories with at least 2 patients): Primary Dataset, Double-Blind Treatment Phase

System Organ Class MedDRA Preferred Term	Placebo (N=1515) n (%)		NB32 (N=2545) n (%)		Total NB (N=3239) n (%)	
Patients with any SAE	**25**	**(1.7%)**	**64**	**(2.5%)**	**74**	**(2.3%)**
Infections and infestations	4	(0.3%)	13	(0.5%)	16	(0.5%)
Cellulitis	2	(0.1%)	3	(0.1%)	3	(<0.1%)
Diverticulitis	0		1	(<0.1%)	2	(<0.1%)
Gastroenteritis viral	0		1	(<0.1%)	2	(<0.1%)
Staphylococcal infection	1	(<0.1%)	2	(<0.1%)	2	(<0.1%)
Bacterial infection	0		1	(<0.1%)	1	(<0.1%)
Bronchitis	0		1	(<0.1%)	1	(<0.1%)
Bursitis infective	0		1	(<0.1%)	1	(<0.1%)
Enterocolitis infectious	0		1	(<0.1%)	1	(<0.1%)
Gastroenteritis	1	(<0.1%)	1	(<0.1%)	1	(<0.1%)
Infection	0		0		1	(<0.1%)
Lobar pneumonia	0		1	(<0.1%)	1	(<0.1%)
Meningitis viral	0		1	(<0.1%)	1	(<0.1%)
Respiratory tract infection viral	0		1	(<0.1%)	1	(<0.1%)
Urinary tract infection	0		1	(<0.1%)	1	(<0.1%)
Hepatobiliary disorders	1	(<0.1%)	9	(0.4%)	10	(0.3%)
Cholecystitis	1	(<0.1%)	6	(0.2%)	6	(0.2%)
Cholecystitis chronic	0		1	(<0.1%)	2	(<0.1%)
Biliary colic	0		1	(<0.1%)	1	(<0.1%)
Cholelithiasis	0		1	(<0.1%)	1	(<0.1%)
Hepatitis cholestatic	0		1	(<0.1%)	1	(<0.1%)
Gastrointestinal disorders	1	(<0.1%)	5	(0.2%)	7	(0.2%)
Gastrointestinal haemorrhage	0		1	(<0.1%)	2	(<0.1%)
Small intestinal obstruction	1	(<0.1%)	1	(<0.1%)	2	(<0.1%)
Abdominal pain	0		1	(<0.1%)	1	(<0.1%)
Duodenal ulcer	0		1	(<0.1%)	1	(<0.1%)
Epiploic appendagitis	0		1	(<0.1%)	1	(<0.1%)
Inguinal hernia, obstructive	0		1	(<0.1%)	1	(<0.1%)
Injury, poisoning and procedural complications	3	(0.2%)	5	(0.2%)	7	(0.2%)
Ankle fracture	1	(<0.1%)	0		1	(<0.1%)
Compression fracture	0		1	(<0.1%)	1	(<0.1%)
Foot fracture	0		0		1	(<0.1%)
Joint dislocation	0		0		1	(<0.1%)
Joint injury	0		1	(<0.1%)	1	(<0.1%)
Snake bite	0		1	(<0.1%)	1	(<0.1%)
Tendon rupture	0		1	(<0.1%)	1	(<0.1%)
Whiplash injury	0		1	(<0.1%)	1	(<0.1%)
Rib fracture	1	(<0.1%)	0		0	
Spinal fracture	1	(<0.1%)	0		0	
Tibia fracture	1	(<0.1%)	0		0	

Table 22 Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (includes SOC categories with at least 2 patients): Primary Dataset, Double-Blind Treatment Phase (*Continued*)

System Organ Class MedDRA Preferred Term	Placebo (N=1515) n (%)		NB32 (N=2545) n (%)		Total NB (N=3239) n (%)	
Nervous system disorders	3	(0.2%)	7	(0.3%)	7	(0.2%)
Syncope	0		2	(<0.1%)	2	(<0.1%)
Convulsion	0		1	(<0.1%)	1	(<0.1%)
Grand mal convulsion	0		1	(<0.1%)	1	(<0.1%)
Migraine	0		1	(<0.1%)	1	(<0.1%)
Paraesthesia	0		1	(<0.1%)	1	(<0.1%)
Radiculopathy	0		1	(<0.1%)	1	(<0.1%)
Cerebrovascular accident	1	(<0.1%)	0		0	
Cervical myelopathy	1	(<0.1%)	0		0	
Dizziness	1	(<0.1%)	0		0	
Cardiac disorders	4	(0.3%)	6	(0.2%)	6	(0.2%)
Myocardial infarction	0		3	(0.1%)	3	(<0.1%)
Cardiac failure	0		1	(<0.1%)	1	(<0.1%)
Coronary artery occlusion	0		1	(<0.1%)	1	(<0.1%)
Palpitations	0		1	(<0.1%)	1	(<0.1%)
Angina pectoris	2	(0.1%)	0		0	
Arrhythmia	1	(<0.1%)	0		0	
Atrial fibrillation	2	(0.1%)	0		0	
Pericardial effusion	1	(<0.1%)	0		0	
Respiratory, thoracic and mediastinal disorders	0		6	(0.2%)	6	(0.2%)
Asthma	0		1	(<0.1%)	1	(<0.1%)
Bronchospasm	0		1	(<0.1%)	1	(<0.1%)
Chronic obstructive pulmonary disease	0		1	(<0.1%)	1	(<0.1%)
Dyspnoea exertional	0		1	(<0.1%)	1	(<0.1%)
Dyspnoea	0		1	(<0.1%)	1	(<0.1%)
Pulmonary embolism	0		1	(<0.1%)	1	(<0.1%)
General disorders and administration site conditions	3	(0.2%)	3	(0.1%)	5	(0.2%)
Non-cardiac chest pain	1	(<0.1%)	2	(<0.1%)	3	(<0.1%)
Chest pain	1	(<0.1%)	1	(<0.1%)	2	(<0.1%)
Chest discomfort	1	(<0.1%)	0		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	(0.2%)	4	(0.2%)	5	(0.2%)
Breast cancer in situ	0		0		1	(<0.1%)
Breast cancer	1	(<0.1%)	1	(<0.1%)	1	(<0.1%)
Colon cancer	0		1	(<0.1%)	1	(<0.1%)
Meningioma	0		1	(<0.1%)	1	(<0.1%)
Multiple myeloma	0		1	(<0.1%)	1	(<0.1%)
Oesophageal carcinoma	1	(<0.1%)	0		0	
Uterine leiomyoma	1	(<0.1%)	0		0	
Musculoskeletal and connective tissue disorders	0		3	(0.1%)	3	(<0.1%)
Intervertebral disc protrusion	0		2	(<0.1%)	2	(<0.1%)
Back pain	0		1	(<0.1%)	1	(<0.1%)
Rotator cuff syndrome	0		1	(<0.1%)	1	(<0.1%)

Table 22 Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (includes SOC categories with at least 2 patients): Primary Dataset, Double-Blind Treatment Phase (*Continued*)

System Organ Class MedDRA Preferred Term	Placebo (N=1515) n (%)		NB32 (N=2545) n (%)		Total NB (N=3239) n (%)	
Renal and urinary disorders	1	(<0.1%)	3	(0.1%)	3	(<0.1%)
Calculus ureteric	1	(<0.1%)	2	(<0.1%)	2	(<0.1%)
Nephrolithiasis	0		1	(<0.1%)	1	(<0.1%)
Reproductive system and breast disorders	2	(0.1%)	3	(0.1%)	3	(<0.1%)
Menorrhagia	1	(<0.1%)	1	(<0.1%)	1	(<0.1%)
Ovarian cyst	0		1	(<0.1%)	1	(<0.1%)
Uterine prolapse	0		1	(<0.1%)	1	(<0.1%)
Ovarian mass	1	(<0.1%)	0		0	
Metabolism and nutrition disorders	0		2	(<0.1%)	2	(<0.1%)
Dehydration	0		2	(<0.1%)	2	(<0.1%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SAE= serious adverse event; SOC=system organ class; Total NB=all doses of combination naltrexone and bupropion treatment.

7.4.4 Adverse Events Leading to Discontinuation

In the Primary Dataset, 24% of patients receiving NB and 12% of patients receiving placebo discontinued treatment due to an AE. The most common AEs leading to discontinuation in NB-treated patients, which were greater than placebo, were nausea, headache, dizziness, and vomiting (Table 23). Most of the common AEs leading to discontinuation were among the common AEs (Table 18); as noted earlier, these events leading to discontinuation were consistent with the AE profiles for the individual components of NB. In general, the incidence of discontinuation due to an AE was similar among NB dose groups.

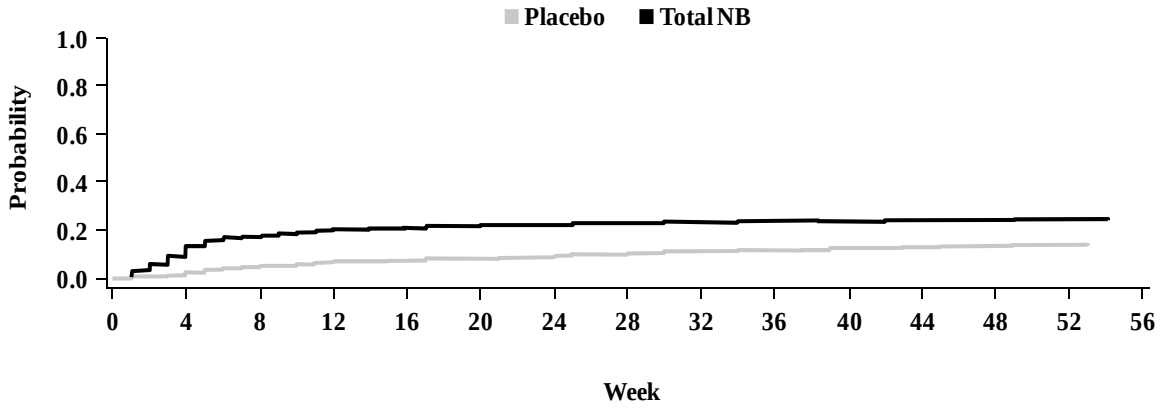
Table 23 Adverse Events Leading to Treatment Discontinuation in ≥0.5% of Patients in the Total NB Group: Primary Dataset, Double-Blind Treatment Phase

MedDRA Preferred Term	Placebo (N=1515) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Patients discontinuing treatment due to any AE	**181 (11.9%)**	**612 (24.0%)**	**771 (23.8%)**
Nausea	3 (0.2%)	160 (6.3%)	203 (6.3%)
Headache	9 (0.6%)	43 (1.7%)	55 (1.7%)
Dizziness	5 (0.3%)	23 (0.9%)	42 (1.3%)
Vomiting	1 (<0.1%)	28 (1.1%)	35 (1.1%)
Insomnia	7 (0.5%)	17 (0.7%)	23 (0.7%)
Anxiety	10 (0.7%)	19 (0.7%)	21 (0.6%)
Urticaria	4 (0.3%)	16 (0.6%)	19 (0.6%)
Depression	13 (0.9%)	10 (0.4%)	16 (0.5%)

Note: Includes only adverse events with 'drug stopped (primary)' as the reason for treatment discontinuation.
Abbreviations: AE= adverse event; MedDRA=Medical Dictionary for Regulatory Activities; Total NB=all doses of combination naltrexone and bupropion treatment.

NB-treated patients who discontinued due to an AE tended to discontinue early in treatment (Figure 27). In the dose-escalation phase (Week 0 to Week 4/5), 17% of patients receiving NB and 4% of patients receiving placebo discontinued treatment due to an AE, and the most common AEs leading to discontinuation (nausea, headache, dizziness, and vomiting) were consistent with those identified above. In the maintenance treatment phase (post Week 4/5), the proportion of patients discontinuing treatment due to an AE was similar between treatment groups (6.4% Total NB, 7.5% placebo).

Figure 27 Discontinuations due to an Adverse Event by Week: Primary Dataset, Double-Blind Treatment Phase



Event probabilities are based on the Kaplan-Meier method. Stratified logrank test is stratified by study.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment.

Differences in the incidence of AEs leading to discontinuation between subgroups of age, sex, ethnicity, race, baseline smoking status, use of antihypertensive medication at baseline, ≥5% weight loss at endpoint, or obesity class were small and not clinically meaningful (see also Appendix 8, Table 74).

7.4.5 Dose Comparison of AEs

Treatment-related AEs (≥2% incidence in any NB group and at least twice the incidence of placebo) were further examined to evaluate which events were dose-related based on their incidence across doses and the known mechanism of action for naltrexone. Data to investigate potential dose-relatedness of AEs have been taken primarily from Study NB-301 (which included NB16 and NB32) as well as the Nondiabetic Dataset (which included NB16, NB32 and NB48). Within each study a single dose of bupropion was used (360 mg in Phase 3 and 400 mg in Study NB-201) and only the naltrexone dose varied (16, 32, 48 mg).

The common AEs with the strongest dose-relationship to naltrexone were nausea, dizziness, vomiting, hot flush, and hyperhidrosis (Table 24). Results from Study NB-301 provided similar results.

Table 24 Dose-Related Treatment-Emergent Adverse Events: Nondiabetic Dataset, Double-Blind Treatment Phase

MedDRA Preferred Term	Placebo (N=1346) n (%)	NB16 (N=633) n (%)	NB32 (N=2212) n (%)	NB48 (N=61) n (%)
Patients with any AE	**993 (73.8%)**	**507 (80.1%)**	**1920 (86.8%)**	**41 (67.2%)**
Nausea	90 (6.7%)	175 (27.6%)	687 (31.1%)	27 (44.3%)
Dizziness	42 (3.1%)	52 (8.2%)	213 (9.6%)	7 (11.5%)
Vomiting	38 (2.8%)	41 (6.5%)	212 (9.6%)	7 (11.5%)
Hot flush	14 (1.0%)	16 (2.5%)	101 (4.6%)	0
Hyperhidrosis	5 (0.4%)	10 (1.6%)	51 (2.3%)	2 (3.3%)
Feeling jittery	5 (0.4%)	3 (0.5%)	33 (1.5%)	2 (3.3%)

Abbreviations: AE= adverse event; MedDRA=Medical Dictionary for Regulatory Activities.

7.4.6 Comparison of Diabetic and Nondiabetic Datasets

7.4.6.1 Most Common Adverse Events

A higher percentage of patients with diabetes reported at least one AE in both the NB32 group (90.4%) and placebo group (85.2%) than in patients without diabetes (86.8% and 73.8%, respectively; Table 25). This result is not unexpected given that, on average, the patients with diabetes were older, had more comorbidities (particularly hypertension and dyslipidemia; Table 8) and were using more concomitant medications (most commonly antihypertensive agents, statins, oral antidiabetic agents and platelet aggregation inhibitors) compared with non-diabetic patients. As with the Primary Dataset, a higher incidence of AEs occurred during the dose-escalation phase for NB32-treated than placebo-treated patients in both the Diabetic and Nondiabetic Datasets. This difference resolved during the maintenance phase, where no substantive differences were noted in the incidence of AEs between the NB32 group and the placebo group in both the Diabetic Dataset (65.2% and 75.7%, respectively) and Nondiabetic Dataset (61.8% and 62.8%, respectively).

Table 25 Common Treatment-Emergent Adverse Events (≥5% in NB32 Group and Greater than Placebo): Nondiabetic and Diabetic Datasets, Double-Blind Treatment Phase

	Nondiabetic Dataset		Diabetic Dataset	
MedDRA Preferred Term	**Placebo (N=1346) n (%)**	**NB32 (N=2212) n (%)**	**Placebo (N=169) n (%)**	**NB32 (N=333) n (%)**
Patients with any AE	**993 (73.8%)**	**1920 (86.8%)**	**144 (85.2%)**	**301 (90.4%)**
Nausea	**90 (6.7%)**	**687 (31.1%)**	**12 (7.1%)**	**141 (42.3%)**
Vomiting	**38 (2.8%)**	**212 (9.6%)**	**6 (3.6%)**	**61 (18.3%)**
Constipation	**97 (7.2%)**	**430 (19.4%)**	**12 (7.1%)**	**59 (17.7%)**
Diarrhoea	**63 (4.7%)**	**128 (5.8%)**	**16 (9.5%)**	**52 (15.6%)**
Headache	**142 (10.5%)**	**401 (18.1%)**	**15 (8.9%)**	**46 (13.8%)**
Dizziness	**42 (3.1%)**	**213 (9.6%)**	**9 (5.3%)**	**39 (11.7%)**
Insomnia	**80 (5.9%)**	**196 (8.9%)**	**9 (5.3%)**	**37 (11.1%)**
Hypertension	27 (2.0%)	49 (2.2%)	7 (4.1%)	33 (9.9%)
Hypoglycaemia	1 (<0.1%)	2 (<0.1%)	12 (7.1%)	25 (7.5%)
Tremor	6 (0.4%)	81 (3.7%)	4 (2.4%)	22 (6.6%)
Dry mouth	**30 (2.2%)**	**184 (8.3%)**	**5 (3.0%)**	**21 (6.3%)**
Anxiety	41 (3.0%)	90 (4.1%)	2 (1.2%)	18 (5.4%)
Abdominal pain upper	17 (1.3%)	71 (3.2%)	3 (1.8%)	17 (5.1%)

Events in bold are considered to be common (≥5% in NB32 Group and Greater than Placebo) in both datasets.
Abbreviations: AE= adverse event; MedDRA= Medical Dictionary for Regulatory Activities.

The most common AEs in patients with diabetes were the same as those seen in patients without diabetes. In the Nondiabetic Dataset, nausea, vomiting, constipation, diarrhea, headache, dizziness, insomnia, and dry mouth were reported in ≥5% of NB32-treated patients and more commonly than in placebo-treated patients (Table 25). In addition to the eight most common AEs identified in the Nondiabetic Dataset, hypertension, hypoglycemia, tremor, anxiety and upper abdominal pain were also identified as common AEs reported in overweight/obese patients with diabetes.

The relative difference between the NB32 and placebo groups for nausea, vomiting, diarrhea, and hypertension was greater in patients with diabetes than in those without diabetes. The difference for nausea, diarrhea, and vomiting may be explained, in part, by concomitant medications (e.g., metformin) associated with gastrointestinal adverse effects, or interaction with diabetic gastroenteropathy. Gastrointestinal AEs in the NB32 treatment group were more frequent in patients using concomitant metformin than in those without metformin (42.7% vs. 26.8%) and the most commonly observed gastrointestinal AE was nausea (36.6% vs. 22.5%). NB32-treated patients using concomitant metformin also reported vomiting, diarrhea, and dyspepsia more frequently than patients not using metformin.

During Study NB-304, biguanides (e.g., metformin) were used by approximately 80% of all patients (79.6% NB32 and 76.7% placebo) and sulfonylurea medications were used by approximately half of all patients (49.1% NB32 and placebo; Table 9). More placebo-treated patients required rescue medications (i.e., increased dose or introduction of new medications)

for diabetes control during the study compared with NB32-treated patients (35.2% vs. 22.3%). This is in keeping with an increased reporting of AEs pertaining to poor control of diabetes (i.e., increased blood glucose) by patients in the placebo group (18.9%) compared with the NB32 group (7.5%). The incidence of hypoglycemia was low and similar between the two groups (7.5% NB32 vs. 7.1% placebo). One NB-treated patient had a treatment-emergent SAE of grand mal convulsion in the context of probable hypoglycemia (this event is discussed in more detail in Section 7.6.5).

Blood pressure-related AEs (including hypertension and increased blood pressure terms) were more common in patients with diabetes than in patients without diabetes, of note, patients with diabetes had a higher incidence of baseline hypertension (62%) compared with patients without diabetes (approximately 20%). The majority of these events were mild or moderate in severity and infrequently resulted in treatment discontinuation; there were no blood pressure-related SAEs. Relative to placebo, changes in blood pressure in patients with diabetes were generally similar to or less than that observed in patients without diabetes (see Section 7.6.1.1.5).

7.4.6.2 Serious Adverse Events

The proportion of patients experiencing SAEs in the Diabetic Dataset was 3.9% in the NB32 group and 4.7% in the placebo group. This is a slightly higher proportion than in the Nondiabetic Dataset (2.3% NB32, 1.3% placebo).

7.4.6.3 Adverse Events Leading to Discontinuation

In a comparison of the Diabetic and Nondiabetic Datasets, a marginally greater percentage of patients in the Diabetic Dataset (29% NB32, 15% placebo) discontinued treatment due to an AE compared with the Nondiabetic Dataset (23% NB32, 12% placebo). Similar to the pattern noted for the Primary Dataset, the difference between the NB32 and placebo groups in both the Diabetic and Nondiabetic datasets was driven by early discontinuations during dose-escalation. Once a stable daily dose of NB was established and patients entered the maintenance phase, the incidence of AEs leading to treatment discontinuation over the subsequent 52 weeks was slightly lower among patients in the NB32 group compared with patients in the placebo group for both datasets.

Reasons for discontinuation were generally similar to those reported in Section 7.4.4 for the Primary Dataset. A greater proportion of patients who had diabetes discontinued treatment due to nausea (9.6%) and vomiting (3.0%) compared with patients who did not have diabetes (5.8% and 0.8% for nausea and vomiting, respectively).

7.5 Summary of Adverse Events

Conclusions from the AE analyses with regard to the Primary Dataset include:

- No new AEs were observed relative to those commonly associated with the individual components naltrexone and bupropion.

- The most common AEs among NB-treated patients were nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea. These AEs in general occurred

upon initiation of treatment (i.e., during the first 4 weeks of treatment), were mostly mild to moderate in severity, and usually resolved without treatment discontinuation.

- Adverse events were more common among NB-treated patients compared with placebo-treated patients during the first 4 weeks of treatment, corresponding to dose escalation. After dose-escalation, the occurrence of AEs appeared to be generally similar between treatment groups through the remainder of the study period.

- Serious AEs were infrequent and the individual event incidences were generally comparable between treatment groups. Serious AEs occurring in more than two NB-treated patients included cholecystitis/cholecystitis chronic, cellulitis, myocardial infarction, and non-cardiac chest pain. A single death occurred during the clinical development program in an NB-treated patient. This event was considered unlikely related to study treatment by the investigator.

- Adverse events leading to discontinuation of study medication were generally consistent with the most common AEs and consistent with the AE profile of bupropion and naltrexone.

- With the exception of increased rates of dizziness, tremor and hypertension events in the ≥65-year-old age NB group, subgroup analyses for AEs, SAEs, and AEs leading to discontinuation did not identify any clinically meaningful differences.

- The common AEs with the strongest dose-relationship to naltrexone were nausea, dizziness, vomiting, hot flush, and hyperhidrosis.

Conclusions from the AE analyses with regard to the comparison of the Diabetic and Nondiabetic Datasets include:

- The most common AEs were generally similar between the Diabetic and Nondiabetic Datasets. Adverse events that occurred more frequently in patients with diabetes treated with NB included nausea, vomiting, diarrhea, and hypertension. These were rarely severe or led to treatment discontinuation.

- The incidence of SAEs was similar in the Diabetic Dataset for both placebo and NB32.

- The proportion of patients with AEs leading to discontinuation of study medication was slightly greater for the Diabetic Dataset, but the types of events leading to discontinuation were qualitatively consistent with those in the Nondiabetic Dataset.

7.6 Safety Topics of Medical Interest

Safety information collected in the NB clinical development program was evaluated for AE types historically associated with either bupropion or naltrexone therapy or other events of interest characterized in the NB clinical studies. The effects of NB on blood pressure and heart rate, as well as CV events, were examined because of the known hemodynamic effects of bupropion. Neuropsychiatric, including depression and suicidality, and neurologic effects, as well as seizure risk, were also examined due to the known effects of bupropion. The

potential for hepatotoxicity due to naltrexone was examined. In addition, renal disorders; hypersensitivity reaction/skin rash; joint and muscle pain; and sexual dysfunction were further characterized.

Preferred terms were organized into subtopics, Standard MedDRA Queries (SMQs), or targeted medical event (TME) groupings as needed to represent specific medical concepts (Appendix 7).

7.6.1 Blood Pressure and Heart Rate

The active constituents of NB, naltrexone and bupropion, have both been approved in the U.S. for many years, and their respective effects on vital signs have been well characterized. Bupropion, by virtue of its effects as a relatively weak dopamine and norepinephrine reuptake inhibitor, has sympathomimetic properties, and its observed hemodynamic profile has been well established and is described in the bupropion prescribing information. As a mu opioid receptor antagonist, naltrexone has no sympathomimetic effects, and clinical experience has not revealed consistent effects on vital signs (Thomas et al., 1976; Crabtree, 1984; Ring et al., 2008). Hence, naltrexone is unlikely to be responsible for blood pressure and heart rate effects observed after NB administration.

Clinical findings for vital signs, as well as the effect of weight loss on blood pressure and AEs related to vital signs are discussed in the following sections. Blood pressure and heart rate events are defined by the Hypertension SMQ, Tachyarrhythmia SMQ, and Arrhythmia SMQ terms (see Appendix 7, Table 61).

7.6.1.1 Vital Signs

Vital signs, including heart rate, SBP, and DBP, were measured in a sitting position at every study visit. In all Phase 3 studies, the reported value was an average of three blood pressure and heart rate readings obtained after the patient had been sitting for at least 5 minutes to minimize measurement variability.

7.6.1.1.1 Mean Blood Pressure and Heart Rate Over Time

In the Total NB group, mean SBP and DBP showed initial increases of approximately 1 mm Hg at Weeks 4 and 8. Mean blood pressure decreased below baseline values after Week 12 and remained below baseline through Week 56. After 28 weeks of treatment, average changes in blood pressure from baseline for NB-treated patients were maintained at approximately 1 mm Hg below baseline values. In the placebo group, mean SBP decreased from baseline over time at each timepoint to Week 24, reaching 2 mm Hg below baseline; mean DBP in the placebo group showed a consistent decrease across monthly timepoints of approximately 2 mm Hg below baseline (Figure 28).

Initial increases in SBP and DBP are consistent with the effects of bupropion (Settle et al., 1999, Thase et al., 2008). The gradual decreases in mean blood pressure observed after Week 8 follow the time course of weight loss in the study population and are consistent with the weight loss-related attenuation of the bupropion pressor effect (Section 6.8.3).

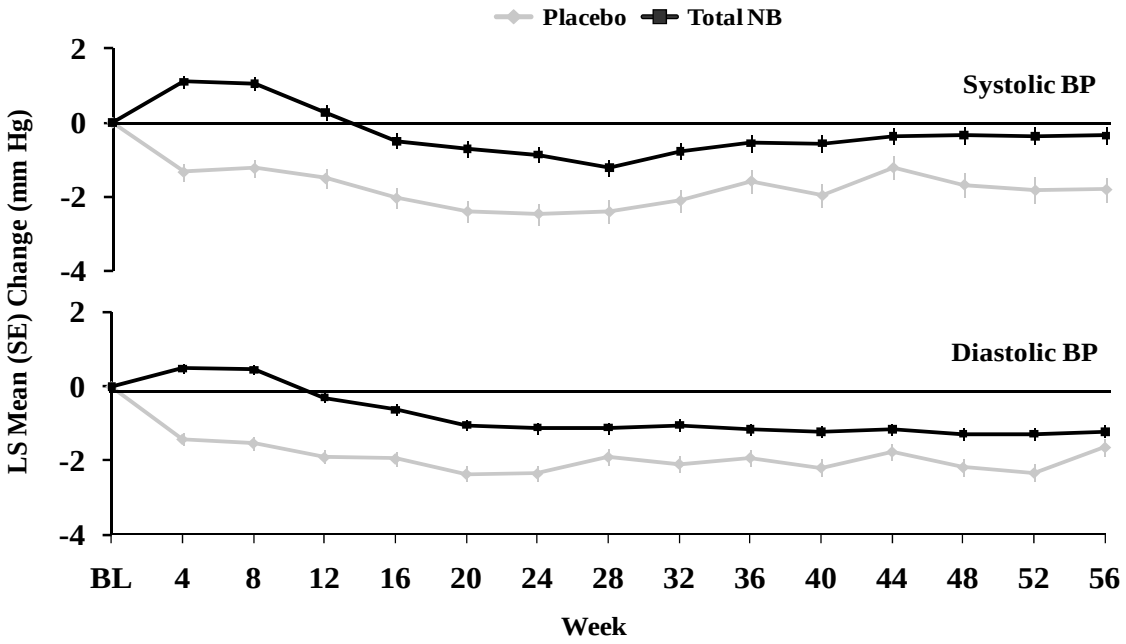
The mean decreases from baseline to endpoint in SBP and DBP were small (<2 mm Hg) for both the Total NB and placebo groups (Table 26). The mean change from baseline to

maximum SBP was higher in the Total NB group at approximately 9 mm Hg compared with the placebo group at approximately 7 mm Hg (Table 27). Mean change from baseline to maximum DBP was similar between groups, increasing by approximately 6 mm Hg in the Total NB group and 5 mm Hg in the placebo group (Table 27).

Mean heart rate in the placebo group generally fluctuated from baseline by ±1 bpm, while mean heart rate in the Total NB group from Week 4 through Week 56 was increased above baseline by approximately 1-3 bpm (range: 0.3 bpm to 2.5 bpm) with no apparent pattern over time (Figure 29). Mean heart rate values were lowest at Weeks 28 and 56 in both treatment groups, which could be attributed to these visits requiring the patients to be in clinic for a longer period of time, allowing the patient to become more relaxed before the measurements were taken.

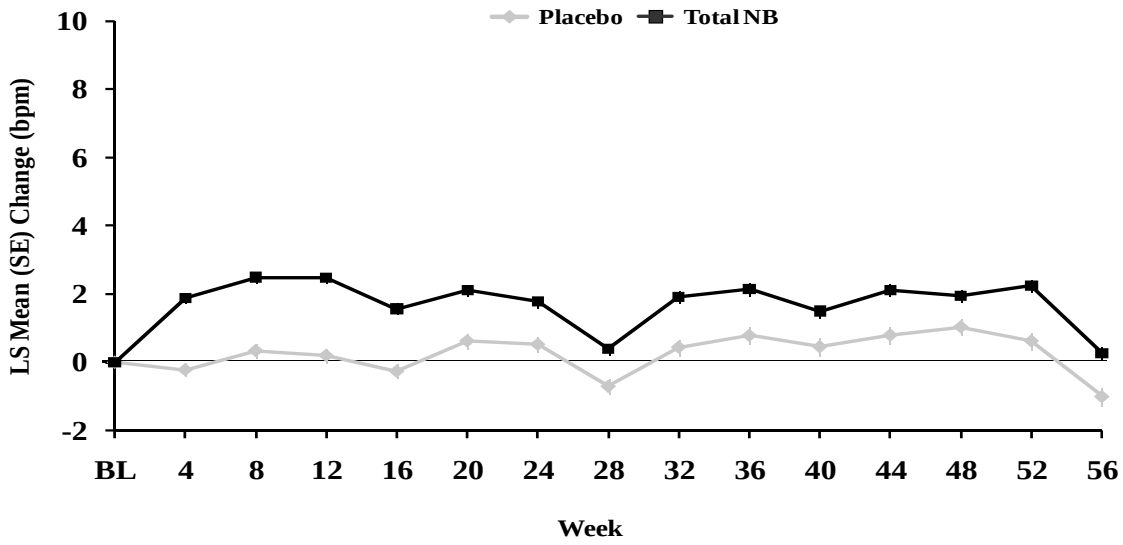
The mean change from baseline to endpoint in heart rate was small (±1 bpm) in both the Total NB (0.94 bpm) and the placebo (-0.20 bpm) groups. The mean change from baseline to maximum in heart rate was similar between groups, increasing by approximately 9 bpm in the Total NB group and 8 bpm in the placebo group (Table 27).

Figure 28 Blood Pressure (mm Hg), Repeated Measures Analysis of Mean Change from Baseline to Each Visit: Primary Dataset, Double-Blind Treatment Phase



Repeated measures mixed effect model: factors in the model included random subject effects; fixed class effects for study, treatment, time (i.e., week), and treatment-by-time interaction; and baseline measurement as the covariate.
Abbreviations: BP=blood pressure; Total NB=all doses of combination naltrexone and bupropion treatment; SE=standard error.

Figure 29 Heart Rate (bpm), Repeated Measures Analysis of Mean Change from Baseline to Each Visit: Primary Dataset, Double-Blind Treatment Phase



Repeated measures mixed effect model: factors in the model included random subject effects; fixed class effects for study, treatment, time (i.e., week), and treatment-by-time interaction; and baseline measurement as the covariate.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment; SE=standard error.

Table 26 Mean Change from Baseline to Endpoint in Vital Signs: Primary Dataset, Double-Blind Treatment Phase (LOCF)

	Placebo (N=1515) mean±SD	NB32 (N=2545) mean±SD	Total NB (N=3239) mean±SD
Patients with post-BL measurement	**1419**	**2226**	**2812**
Systolic Blood Pressure (mm Hg)			
Baseline	119.10±10.39	118.99±10.41	118.96±10.35
Week 56	117.46±11.35	118.53±11.99	118.68±11.82
Mean Change from Baseline	-1.64±9.95	-0.46±10.16	-0.28±10.07
Diastolic Blood Pressure (mm Hg)			
Baseline	77.07±6.93	77.16±7.22	76.98±7.23
Week 56	75.80±7.71	76.53±7.85	76.45±7.82
Mean Change from Baseline	-1.27±7.31	-0.63±7.20	-0.53±7.19
Heart Rate (bpm)			
Baseline	71.49±8.42	71.49±8.51	71.39±8.54
Week 56	71.29±8.57	72.25±8.93	72.33±8.80
Mean Change from Baseline	-0.20±7.79	0.76±7.94	0.94±7.95

Endpoint was Week 56 for the four Phase 3 studies and Week 24 for Study NB-201.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment; SD=standard deviation.

Table 27 Mean Change from Baseline to Maximum Value in Vital Signs: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515) mean±SD	NB32 (N=2545) mean±SD	Total NB (N=3239) mean±SD
Patients with post-BL measurement	**1419**	**2226**	**2812**
Systolic Blood Pressure (mm Hg)			
Baseline	119.10±10.39	118.99±10.41	118.96±10.35
Maximum	126.30±11.64	127.51±12.17	127.47±12.02
Mean Change from Baseline	7.20±9.40	8.51±10.10	8.52±9.95
Diastolic Blood Pressure (mm Hg)			
Baseline	77.07±6.93	77.16±7.22	76.98±7.23
Maximum	81.89±7.00	83.06±7.52	82.87±7.50
Mean Change from Baseline	4.82±6.49	5.90±6.83	5.89±6.75
Heart Rate (bpm)			
Baseline	71.49±8.42	71.49±8.51	71.39±8.54
Maximum	79.31±9.25	80.56±9.43	80.46±9.35
Mean Change from Baseline	7.83±8.18	9.06±8.62	9.08±8.62

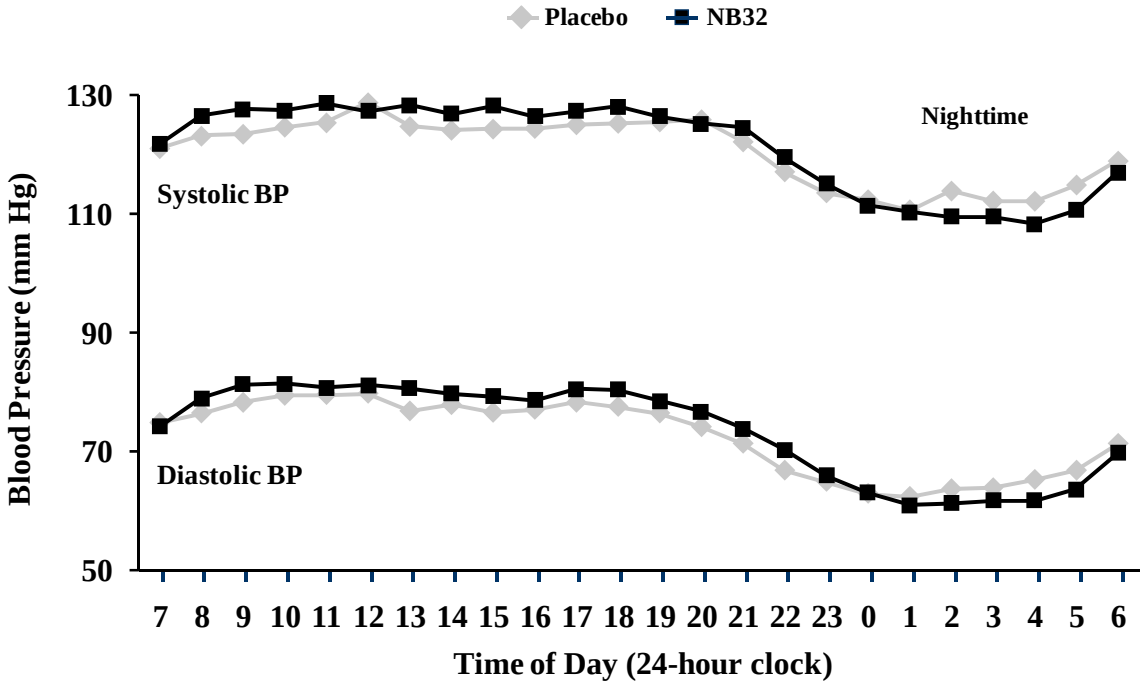
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment; SD=standard deviation.

7.6.1.1.2 Ambulatory Blood Pressure and Heart Rate

A substudy of NB-303 was conducted to examine hourly ambulatory blood pressure and heart rate over 24-hour periods at baseline, Week 24, and Week 52. The assessments included average daytime (7:00 A.M.-10:00 P.M., inclusive) and nighttime (10:00 P.M.-7:00 A.M.) blood pressure and heart rate. The substudy enrolled overweight and obese patients treated with NB32 (n=121) or placebo (n=59). Consistent with other safety analyses, NB32 patients re-randomized to NB48 in Study NB-303 were included in the NB32 group.

The 24-hour SBP and DBP patterns were similar between NB- and placebo-treated patients (Figure 30). The normal circadian variation of blood pressure, including a nocturnal decrease, was maintained in both treatment groups. This is particularly relevant as a loss of the nocturnal lowering in blood pressure is regarded as an important predictor of cardiovascular outcome (Fagard et al., 2008; Dolan et al., 2005).

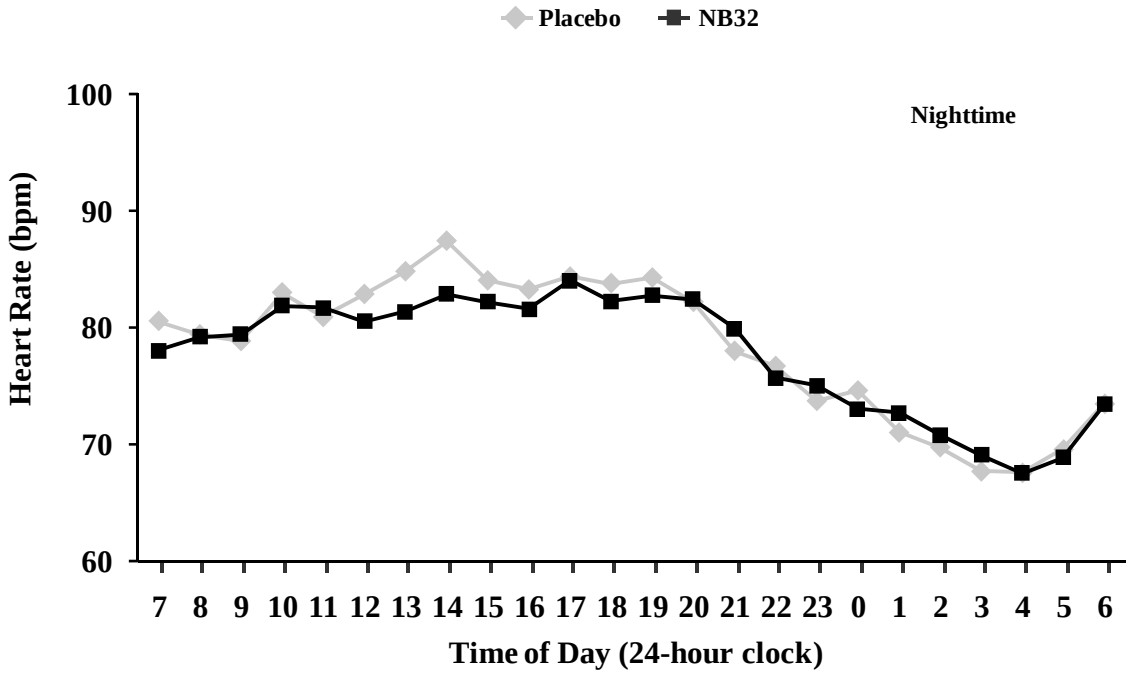
Figure 30 Mean Hourly Blood Pressure, Week 52: ABPM Substudy Analysis Set (Study NB-303 ABPM)



Time 0 represents 12:00 A.M. on the 24-hour clock. The start time of the 24-hour ABPM monitoring period for most patients on this figure is between 7:00 A.M. and 10:00 A.M. Data are LS mean.
Abbreviations: ABPM=ambulatory blood pressure monitoring; BP=blood pressure.

The LS mean change in the average 24-hour heart rate was similar between groups (Figure 31) and largely unchanged from baseline to Week 52 (NB32: 0.05 bpm; placebo: -0.52 bpm), as was the average daytime and nighttime heart rate (Table 28).

Figure 31 Mean Hourly Heart Rate, Week 52: ABPM Substudy Analysis Set (Study NB-303 ABPM)



Time 0 represents 12:00 A.M. on the 24-hour clock. The start time of the 24-hour ABPM monitoring period for most patients on this figure is between 7:00 A.M. and 10:00 A.M. Data are LS mean.
Abbreviations: ABPM=ambulatory blood pressure monitoring.

At Week 52, the LS mean change from baseline in average daytime SBP or DBP showed little or no change from baseline in the NB32 group (approximately 1 mm Hg or less compared with approximately 3 mm Hg or less in the placebo group; Table 28).

Table 28 Mean Change from Baseline to Week 52 in Average Daytime, Nighttime, and 24-hour Systolic and Diastolic Blood Pressures: ABPM Substudy Analysis Set (Study NB-303 ABPM) (LOCF)

LS Mean Change from Baseline	PBO (N=38) LS mean (SE)	NB32 (N=79) LS mean (SE)
Systolic Blood Pressure (mm Hg)		
Daytime	-3.09 (1.36)	0.17 (0.94)
Nighttime	-2.07 (1.43)	-1.63 (0.99)
24-hour	-2.82 (1.28)	-0.21 (0.89)
Diastolic Blood Pressure (mm Hg)		
Daytime	-1.90 (0.97)	1.16 (0.67)
Nighttime	-1.89 (1.00)	-0.36 (0.69)
24-hour	-2.06 (0.86)	0.82 (0.59)
Heart Rate (bpm)		
Daytime	0.40 (1.15)	0.41 (0.80)
Nighttime	-1.88 (1.09)	-1.05 (0.76)
24-hour	-0.52 (1.04)	0.05 (0.72)

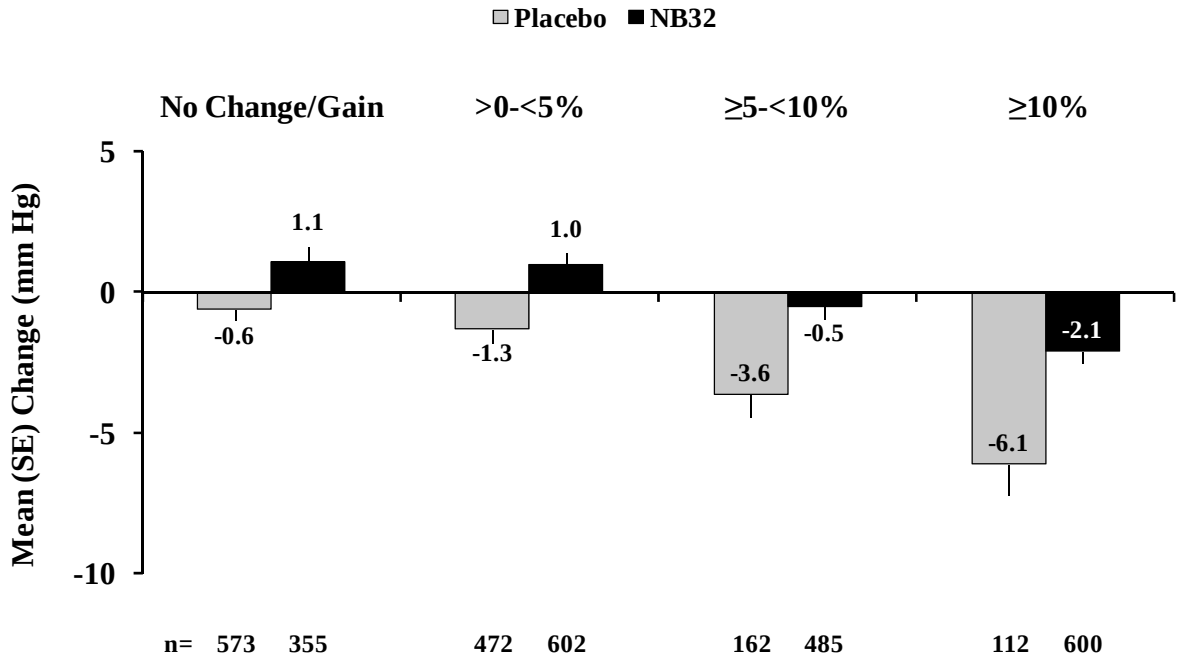
Abbreviations: ABPM=ambulatory blood pressure monitoring; SE=standard error.

The ABPM results are consistent with those reported by Settle et al., (1999) as well as those of Thase et al., (2008) who studied the effect of doses of bupropion of 300-400 mg in otherwise healthy adults with mild untreated hypertension. The addition of naltrexone to bupropion treatment appears to have no effect on the known effects of bupropion on blood pressure.

7.6.1.1.3 Effect of Weight Change on Blood Pressure

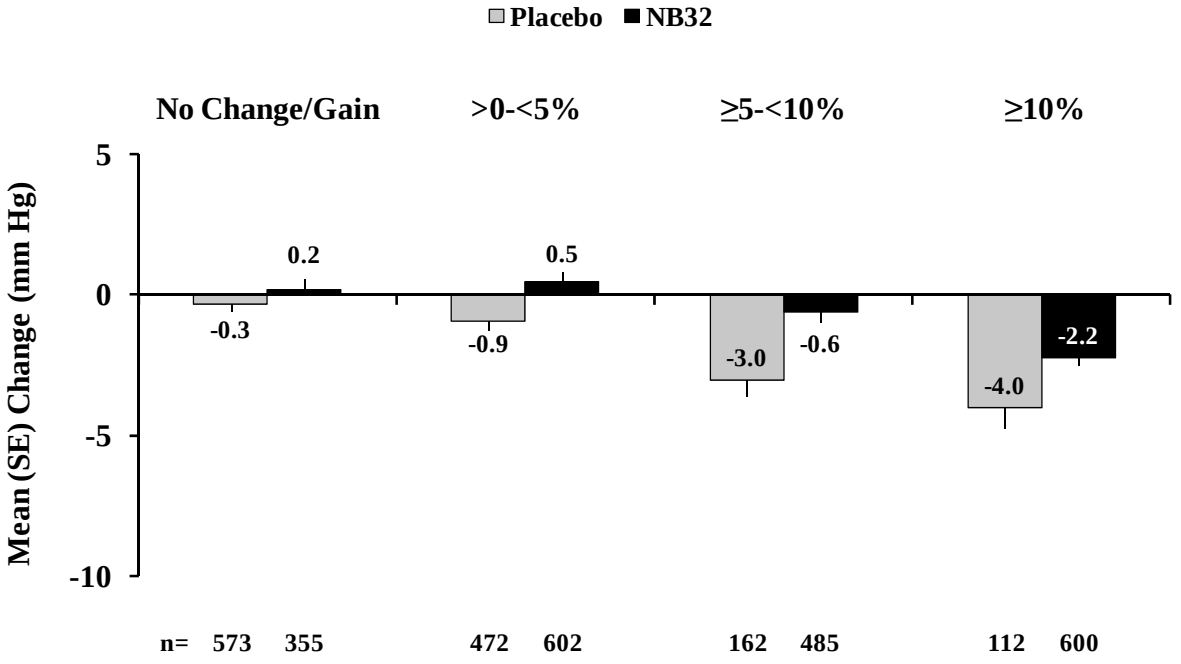
In the Phase 3 NB program, mean blood pressure decreased with increasing degrees of weight loss with both NB and placebo treatment. Among the NB32-treated patients, decreases in mean SBP and DBP were observed in patients achieving ≥5% weight loss, but not in those with <5% weight loss (at endpoint, SBP: -1.4 mm Hg vs. 1.0 mm Hg; DBP: -1.5 mm Hg vs. 0.4 mm Hg; [mITT-LOCF]). Placebo-treated patients experienced greater reductions of mean blood pressure within each weight loss category compared with NB32-treated patients. Consistent with these results, a pooled analysis across the Phase 3 studies of mean changes in SBP (Figure 32), DBP (Figure 33) and heart rate (Figure 34) by weight loss category indicate greater decreases from baseline in blood pressure in patients experiencing greater degrees of weight loss for both NB32 and placebo groups. Similar patterns were observed in the full analysis set and in the completers analysis. Of note, a greater proportion of NB-treated patients achieved categorical weight loss thresholds compared to placebo.

Figure 32 Systolic Blood Pressure, Mean Change from Baseline to Week 56 Endpoint for all Phase 3 Studies (Pooled) by Weight Loss Category (mITT-LOCF)



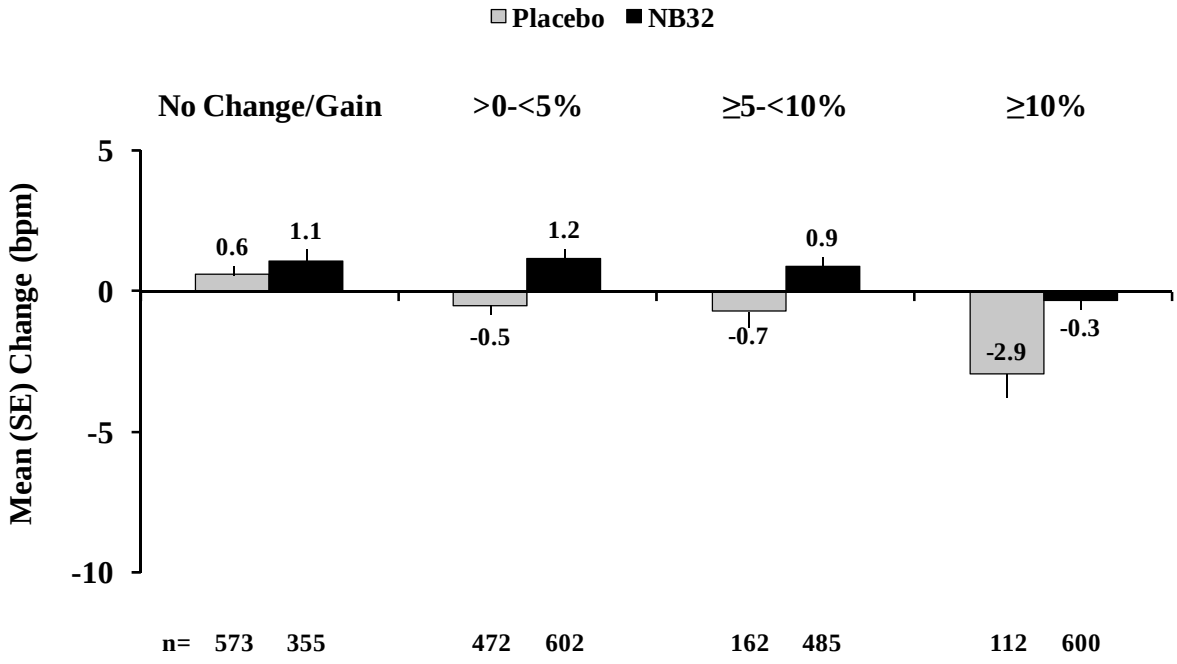
Abbreviations: SE=standard error.

Figure 33 Diastolic Blood Pressure, Mean Change from Baseline to Week 56 Endpoint for all Phase 3 Studies (Pooled) by Weight Loss Category (mITT-LOCF)



Abbreviations: SE=standard error.

Figure 34 Heart Rate, Mean Change from Baseline to Week 56 Endpoint for all Phase 3 Studies (Pooled) by Weight Loss Category (mITT-LOCF)



Abbreviations: SE=standard error.

7.6.1.1.4 Blood Pressure and Heart Rate Outlier Values

Outlier values for blood pressure and heart rate during the studies were defined on the basis of two consecutive assessments or a single measurement if it represented the final visit. Outlier thresholds for blood pressure were defined as absolute treatment-emergent increases based on The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) criteria (systolic: ≥140, ≥160 mm Hg; diastolic: ≥90, ≥100 mm Hg). Heart rate outliers were defined as ≥100 or ≥110 bpm. Relative increases were defined as ≥5 mm Hg (diastolic), ≥10 mm Hg (systolic), and ≥10 bpm (heart rate) above baseline. The incidences of SBP and DBP increases above prespecified criteria were generally higher in the Total NB group than the placebo group for elevations above baseline and increases above threshold (Table 29).

Table 29 Incidence of Treatment-Emergent Increases in Systolic and Diastolic Blood Pressure: Primary Dataset, Double-Blind Treatment Phase

Category	Placebo (N=1515) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Patients with post-BL measurement	**1419**	**2226**	**2812**
Systolic Blood Pressure			
≥2 values ≥140 mm Hg	56 (3.9%)	150 (6.7%)	180 (6.4%)
≥2 values ≥160 mm Hg	2 (0.1%)	5 (0.2%)	5 (0.2%)
≥2 values ≥10 mm Hg over BL	264 (18.6%)	559 (25.1%)	703 (25.0%)
Diastolic Blood Pressure			
≥2 values ≥90 mm Hg	64 (4.5%)	145 (6.5%)	180 (6.4%)
≥2 values ≥100 mm Hg	6 (0.4%)	9 (0.4%)	12 (0.4%)
≥2 values ≥5 mm Hg over BL	406 (28.6%)	825 (37.1%)	1039 (36.9%)

At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment.

The incidence of heart rate increases to ≥100 bpm at two consecutive visits or the final visit was seen in 1.0% of the Total NB group and 0.5% of the placebo group (Table 30) and a ≥110 bpm increase in heart rate at two consecutive visits or the final visit was seen only in the placebo group (one patient). Increases in heart rate from baseline (≥10 bpm) were common in both groups, but were observed at higher incidences in NB-treated patients. Increases in heart rate were rarely associated with AEs.

Table 30 Incidence of Treatment-Emergent Increases in Heart Rate: Primary Dataset, Double-Blind Treatment Phase

Category	Placebo (N=1515) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Patients with post-BL measurement	**1419**	**2226**	**2812**
≥2 values ≥100 bpm	7 (0.5%)	24 (1.1%)	27 (1.0%)
≥2 values ≥110 bpm	1 (<0.1%)	0	0
≥2 values ≥10 bpm over BL	269 (19.0%)	575 (25.8%)	741 (26.4%)

At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment.

7.6.1.1.5 Comparison of Diabetic and Nondiabetic Datasets

Blood Pressure

The incidence of hypertension at baseline, defined as a pre-existing diagnosis of hypertension or the use of anti-hypertensive medications at baseline, was higher in patients with diabetes (63.4% and 60.9% in the NB32 and placebo groups, respectively) compared with patients without diabetes (19.7% and 19.6% in the NB32 and placebo groups, respectively). The mean SBP was higher at baseline in the Diabetic Dataset consistent with the inclusion criteria for the diabetes study, which allowed for higher baseline blood pressure values (<145 mm Hg [systolic], <95 mm Hg [diastolic]). Of note, the Diabetic Dataset also had a higher proportion of men, was older, and had a higher frequency of dyslipidemia at baseline

(Study NB-304; Section 6.7, Table 8). As expected, patients with diabetes were also more likely to be taking anti-hypertensive medications, statins, and platelet aggregation inhibitors.

Patients with diabetes had similar mean changes from baseline to endpoint in SBP and DBP compared with patients without diabetes for both the NB32 and placebo groups.

The incidences of SBP and DBP increases above prespecified criteria (defined in Section 7.6.1.1.4) were higher in the Diabetic Dataset compared with the Nondiabetic Dataset in both the NB32 and placebo groups (Table 31). Relative differences in the incidence of outlier values between the NB32 and placebo groups were comparable for the Diabetic and Nondiabetic Datasets.

Table 31 Incidence of Treatment-Emergent Increases in Systolic and Diastolic Blood Pressure: Diabetic and Nondiabetic Datasets, Double-Blind Treatment Phase

	Nondiabetic Dataset		Diabetic Dataset	
Category	**Placebo (N=1346) n (%)**	**NB32 (N=2212) n (%)**	**Placebo (N=169) n (%)**	**NB32 (N=333) n (%)**
Patients with post-BL measurement	1258	1933	161	293
Systolic Blood Pressure				
≥2 values ≥140 mm Hg	40 (3.2%)	100 (5.2%)	16 (9.9%)	50 (17.1%)
≥2 values ≥160 mm Hg	1 (<0.1%)	2 (0.1%)	1 (0.6%)	3 (1.0%)
≥2 values ≥10 mm Hg over BL	222 (17.6%)	474 (24.5%)	42 (26.1%)	85 (29.0%)
Diastolic Blood Pressure				
≥2 values ≥90 mm Hg	54 (4.3%)	126 (6.5%)	10 (6.2%)	19 (6.5%)
≥2 values ≥100 mm Hg	5 (0.4%)	6 (0.3%)	1 (0.6%)	3 (1.0%)
≥2 values ≥5 mm Hg over BL	354 (28.1%)	716 (37.0%)	52 (32.3%)	109 (37.2%)

At least two consecutive treatment-emergent values or a single treatment-emergent value if last.

Heart Rate

There were no meaningful differences in patients with and without diabetes with regard to mean change from baseline in heart rate or treatment-emergent increases above prespecified criteria (Table 32). Increases in heart rate were rarely associated with AEs.

Table 32 Incidence of Treatment-Emergent Increases in Heart Rate: Diabetic and Nondiabetic Datasets, Double-Blind Treatment Phase

	Nondiabetic Dataset		Diabetic Dataset	
Category	**Placebo (N=1346) n (%)**	**NB32 (N=2212) n (%)**	**Placebo (N=169) n (%)**	**NB32 (N=333) n (%)**
Patients with ≥1 post-BL measurement	1258	1933	161	293
≥2 values ≥100 bpm	5 (0.4%)	24 (1.0%)	2 (1.2%)	3 (1.0%)
≥2 values ≥110 bpm	1 (<0.1%)	0	0	0
≥2 values ≥10 bpm over BL	234 (18.6%)	507 (26.2%)	35 (21.7%)	68 (23.2%)

At least two consecutive treatment-emergent values or a single treatment-emergent value if last.

7.6.1.1.6 Blood Pressure and Heart Rate in Subpopulations

Increasing age, males, non-Hispanics, Blacks, patients with a prior CV history or a medical history of dyslipidemia, and patients receiving anti-hypertensive medications at baseline more commonly experienced outlier values in SBP or DBP; males and younger patients had increased rates of heart rate outliers; similar patterns were observed for both NB and placebo treatment.

In subgroup analyses evaluating prespecified outlier criteria for pulse, patients receiving NB and having a ≥5% weight loss at endpoint showed increased incidence for pulse increases compared to those patients with ≤5% weight loss at endpoint. Blacks/African Americans receiving NB showed somewhat higher incidences of prespecified systolic blood pressure outlier values compared to other races. Hispanic patients and those with higher BMI receiving NB therapy showed slightly higher incidences in outlier values for diastolic blood pressure. Overall, these differences did not appear clinically significant. Tables for each population are provided in (Appendix 8, Table 75, Table 76, and Table 77).

7.6.1.2 Blood Pressure and Heart Rate Events

7.6.1.2.1 Hypertension

Hypertension AEs were defined by an SMQ grouping of preferred terms (Appendix 7, Table 61). The absolute incidence of the Hypertension SMQ was greater for NB-treated than placebo-treated patients (Table 33). Of the hypertension-type events, hypertension and blood pressure increased were more likely to occur with NB treatment (Table 33). No blood pressure SAEs were reported and events leading to discontinuation were rare (<1%).

Table 33 Treatment-emergent Hypertension SMQ Adverse Events: Primary Dataset, Double-Blind Treatment Phase

SMQ Preferred Terms	Incidence, n (%)		
	Placebo (N=1515)	NB32 (N=2545)	Total NB (N=3239)
Hypertension SMQ	60 (4.0%)	146 (5.7%)	170 (5.2%)
Hypertension	34 (2.2%)	82 (3.2%)	94 (2.9%)
BP increased	22 (1.5%)	61 (2.4%)	73 (2.3%)
Labile hypertension	0	2 <0.1%)	2 (<0.1%)
Systolic BP increased	2 (0.1%)	1 (<0.1%)	1 (<0.1%)
Diastolic BP increased	2 (0.1%)	1 (<0.1%)	1 (<0.1%)
Hypertension SMQ SAE	0	0	0
Discontinuations due to Hypertension SMQ event	3 (0.2%)	17 (0.7%)	23 (0.7%)

A listing of MedDRA preferred terms for the analysis set is provided in Appendix 7, Table 61.
Abbreviations: BP=blood pressure; SAE=serious adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SMQ= Standard MedDRA Queries; Total NB=all doses of combination naltrexone and bupropion treatment.

The proportion of patients that discontinued due to hypertension was 0.7% in the Total NB group and 0.2% in the placebo group. Medications to control hypertension were taken during the study by a similar proportion of patients in the Total NB and placebo groups (26% and

25%, respectively). The most common classes of antihypertensive medications (used by at least 5% of patients in the Total NB and placebo groups) were:

- Thiazides (e.g., hydrochlorothiazide): 12% each
- Angiotensin-converting enzyme (ACE) inhibitors: 11% vs. 10%, respectively
- Angiotensin II antagonists: 7% vs. 8%, respectively

Calcium channel blockers or beta blockers were each reported in <5% of patients.

7.6.1.2.2 Arrhythmias and Tachyarrhythmia

Arrhythmia and Tachyarrhythmia AEs were defined by an SMQ grouping of preferred terms (Appendix 7, Table 61). The incidence of the Arrhythmia SMQ was slightly greater for NB-treated (5.5%) than placebo-treated patients (4.2%; Table 34). Of the common preferred terms in the Arrhythmia SMQ, palpitations, heart rate increased, and tachycardia were more frequent with NB treatment. Events of palpitations occurred with the greatest treatment difference, 2.4% vs. 0.9%. Palpitations were rarely severe (<0.1% Total NB; none in placebo) and infrequently led to discontinuations (0.3% Total NB; none in placebo). Palpitations were reported along with dizziness in 12 of 90 patients (10 NB patients and 2 placebo patients), but in no instances were these events severe or led to study discontinuation. There is no evidence that palpitations were associated with syncope.

No life-threatening Arrhythmia SMQ events were reported in the Total NB group. There were no important NB effects on ECG morphology, cardiac conduction, or repolarization (Section 7.8). These findings are consistent with the lack of effect of naltrexone or bupropion on cardiac repolarization.

Table 34 Treatment-emergent Arrhythmia SMQ Adverse Events: Primary Dataset, Double-Blind Treatment Phase

SMQ Preferred Terms	Incidence, n (%)		
	Placebo (N=1515)	NB32 (N=2545)	Total NB (N=3239)
Arrhythmia SMQ	63 (4.2%)	142 (5.6%)	179 (5.5%)
Palpitations	13 (0.9%)	54 (2.1%)	77 (2.4%)
Heart rate increased	17 (1.1%)	43 (1.7%)	46 (1.4%)
Tachycardia	2 (0.1%)	16 (0.6%)	20 (0.6%)
Syncope	4 (0.3%)	11 (0.4%)	12 (0.4%)
ECG QT prolonged	4 (0.3%)	5 (0.2%)	8 (0.2%)
ECG abnormal	2 (0.1%)	4 (0.2%)	4 (0.1%)
AV block first degree	5 (0.3%)	2 (<0.1%)	3 (<0.1%)
Sinus bradycardia	0	0	3 (<0.1%)
Atrial fibrillation	4 (0.3%)	2 (<0.1%)	2 (<0.1%)
Bundle branch block right	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)
Extrasystoles	0	2 (<0.1%)	2 (<0.1%)
Supraventricular tachycardia	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)
Ventricular extrasystoles	0	2 (<0.1%)	2 (<0.1%)
Arrhythmia	3 (0.2%)	1 (<0.1%)	1 (<0.1%)
AV block	2 (0.1%)	1 (<0.1%)	1 (<0.1%)
Bradycardia	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Heart rate decreased	0	1 (<0.1%)	1 (<0.1%)
Sinus tachycardia	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Atrial flutter	0	0	1 (<0.1%)
Loss of consciousness	1 (<0.1%)	0	1 (<0.1%)
Arrhythmia supraventricular	1 (<0.1%)	0	0
Bundle branch block left	1 (<0.1%)	0	0
Bundle branch block	1 (<0.1%)	0	0
Heart rate irregular	1 (<0.1%)	0	0
Arrhythmia SMQ SAE	3 (0.2%)	3 (0.1%)	3 (<0.1%)
Syncope	0	2 (<0.1%)	2 (<0.1%)
Palpitations	0	1 (<0.1%)	1 (<0.1%)
Arrhythmias	1 (<0.1%)	0	0
Atrial fibrillation	2 (0.1%)	0	0
Discontinuations due to Arrhythmia SMQ event	8 (0.5%)	12 (0.5%)	20 (0.6%)

A listing of MedDRA preferred terms for the analysis set is provided in Appendix 7, Table 61.
Abbreviations: AV=atrioventricular; ECG=electrocardiogram; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SMQ=Standard MedDRA Queries; Total NB=all doses of combination naltrexone and bupropion treatment.

The Tachyarrhythmia SMQ was also analyzed to further understand the effects of NB when palpitations is not a component of the SMQ. Events in the Tachyarrhythmia SMQ occurred less frequently in the NB group compared with placebo (Table 35).

Table 35 Treatment-emergent Tachyarrhythmia SMQ Adverse Events: Primary Dataset, Double-Blind Treatment Phase

SMQ Preferred Terms	Incidence, n (%)		
	Placebo (N=1515)	NB32 (N=2545)	Total NB (N=3239)
Tachyarrhythmia SMQ	7 (0.5%)	8 (0.3%)	9 (0.3%)
Atrial fibrillation	4 (0.3%)	2 (<0.1%)	2 (<0.1%)
Extrasystoles	0	2 (<0.1%)	2 (<0.1%)
Supraventricular tachycardia	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)
Ventricular extrasystoles	0	2 (<0.1%)	2 (<0.1%)
Sinus tachycardia	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Atrial flutter	0	0	1 (<0.1%)
Arrhythmia supraventricular	1 (<0.1%)	0	0
Tachyarrhythmia SMQ SAE	2 (0.1%)	0	0
Atrial fibrillation	2 (0.1%)	0	0
Discontinuations due to Tachyarrhythmia SMQ event	3 (0.2%)	2 (<0.1%)	2 (<0.1%)

A listing of MedDRA preferred terms for the analysis set is provided in Appendix 7, Table 61.
Abbreviations: BP=blood pressure; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SMQ=Standard MedDRA Queries; Total NB=all doses of combination naltrexone and bupropion treatment.

7.6.2 Cardiovascular Events

Inclusion criteria for the Phase 3 NB clinical studies defined entry blood pressure criteria (<145/95 mm Hg in diabetes patients, ≤140/90 mm Hg for all others) and clinically unremarkable ECGs. Exclusion criteria did not permit serious or active cardiovascular (CV) conditions in the 6 months prior to screening (class III or IV congestive heart failure [CHF], myocardial infarction [MI], angina pectoris, claudication, or acute limb ischemia) or lifetime history of stroke. Examination of baseline medical history terms identified that approximately 29% of patients in both treatment groups had a history of CV disease (using broad definitions) consistent with protocol entry criteria, and that specific prior ischemic coronary artery disease was present in <2% of both groups. Primarily, patients were categorized with a history of CV disease due to reported hypertension (approximately 25% of all patients); all other preferred terms occurred in ≤1.5% of patients.

7.6.2.1 Major Cardiovascular Events

Major adverse cardiovascular events (MACE) were assessed using the "Broad MACE" and "Custom MACE" definitions taken from FDA evaluations of agents for type 2 diabetes. The Broad MACE composite endpoint is the combination of standard MedDRA queries (SMQs) for myocardial infarction (MI), central nervous system hemorrhages, cerebrovascular accident (CVA), and cardiovascular (CV) deaths. The Custom MACE composite endpoint is a subset of Broad MACE that reviewers have considered more likely to represent acute and atherosclerotic CV events. A complete listing of all preferred terms in the broad and custom MACE categories can be found in Appendix 7, Table 63 and Table 64. Although coronary revascularization procedures do not constitute adverse events, they do reflect acute onset or

progression of pre-existing coronary disease. Therefore, the frequency and distribution of these procedures in the NB Clinical Development Program were also evaluated.

Major cardiovascular AEs based on various definitions (broad or custom) with and without revascularization procedures revealed generally balanced event rates between the placebo and NB treatment groups (Table 36). The exposure adjusted incidence rate of MACE events was approximately 0.2/100 patient-years, which is consistent with predicted rates for a female, middle-age, obese population (Willett et al., 1995; Manson et al., 1990). While the results from the NB clinical program do not suggest a specific trend in the data, the limited number of events precludes definitive conclusions regarding the impact of NB on ischemic CV events.

Table 36 Treatment-emergent MACE Assessment: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)	NB32 (N=2545)		Total NB (N=3239)	
	Incidence, n (%)	Incidence, n (%)	Relative Risk (95% CI)[a]	Incidence, n (%)	Relative Risk (95% CI)[a]
Ischemic heart disease SMQ	4 (0.26)	9 (0.35)	1.35 (0.42, 4.31)	9 (0.28)	1.28 (0.39, 4.20)
Broad MACE	2 (0.13)	5 (0.20)	1.55 (0.31, 7.75)	5 (0.15)	1.42 (0.27, 7.53)
Custom MACE+ revascularization	3 (0.20)	4 (0.16)	0.84 (0.20, 3.52)	4 (0.12)	0.75 (0.17, 3.38)
Custom MACE	1 (0.07)	3 (0.12)	1.95 (0.22, 17.29)	3 (0.09)	1.69 (0.17, 17.06)
Nonfatal myocardial infarction[b]	0	2 (0.08)		2 (0.06)	
Cardiovascular death	0	1 (0.04)		1 (0.03)	
Stroke	1 (<0.1)	0		0	

a. RR and CI are calculated using the exact method and stratified by study.
b. One additional nonfatal myocardial infarction occurred >30 days post discontinuation of study in a patient who received NB16 during the treatment phase.

Note: MACE definitions per previous FDA evaluations; Relative risk is exposure adjusted. A listing of MedDRA preferred terms for each analysis set is provided in Appendix 7, Table 63 and Table 64.
Abbreviations: CI=confidence interval; MACE=major adverse cardiovascular event; MedDRA=Medical Dictionary for Regulatory Activities; SMQ=Standard MedDRA Queries; Total NB=all doses of combination naltrexone and bupropion treatment.

Seven patients in the NB Clinical Development Program experienced Major CV events and/or underwent revascularization procedures. Table 37 provides demographic and disease-state information for these patients. Four of seven patients were male and all patients had multiple risk factors for ischemic heart disease; only one patient (Patient 3, fatal myocardial infarction) had treatment-emergent increases in blood pressure recorded near the time of the event.

An eighth patient developed symptoms consistent with gastroesophageal reflux and discontinued NB16 treatment on Day 13. Thirty-six days after the last dose of study drug the patient had a myocardial infarction and underwent right coronary stent procedure. Because the event occurred >7 days after discontinuing the study, this event is not considered treatment-emergent and the patient is not included in the calculation of incidence rates for cardiovascular events. Brief narratives for all patients with Major CV Events are provided after the table.

Table 37 Patients Experiencing Major CV Events and/or Revascularization in the NB Clinical Development Program

Treatment Group	Patient ID/ Study	Age (yrs)/ Sex	Adverse Event (MedDRA Preferred Term)	SAE	MACE category	Other CV AEs (MedDRA Preferred Term)	Intervention	Discontinued Study Drug	Study Day of AE Onset	Selected Comorbidities and Risk Factors	Selected Concomitant Medications
Treatment-Emergent events											
NB32 (N=2545)	1 NB-303	50/F	MI	Y	Broad, Custom	Femoral artery stenosis[a], Coronary artery disease	Drug eluting stent placement to LAD	Y	85	Angina, dyslipidemia hypertension, tobacco use	acetylsalicylic acid, ketocanozole, lisinopril
	2 NB-304	44/M	MI	Y	Broad, Custom	None	Percutaneous coronary intervention of RCA	Y	56	Diabetes, hyperlipidemia, former smoker	glipizide, metformin, pioglitazone, pravastatin, fenofibrate
	3 NB-301	65/M	MI	Y	Broad, Custom	None	None, fatal	Y, fatal	324	Hypertension, idiopathic bradycardia, hypercholesterolemia	allopurinol, acetylsalicylic acid, lovastatin, lisinopril, naproxen sodium
	4 NB-304	59/M	Coronary artery occlusion	Y	Broad	None	Stent to RCA, LAD	N (stopped temporarily)	35	Diabetes, active angina pectoris, hyperlipidemia, hypertension, decreased HDL	nifedipine, metformin, acetylsalicylic acid, rosuvastatin
Placebo (N=1515)	5 NB-303	52/F	Coronary artery disease	N[b]	Excluded from MACE	Dyspnoea, Chest pain	Drug eluting stent placement	Y	144	History of chest pain, hypertension, hyperlipidemia	Atenolol, chlortalidone
	6 NB-304	68/M	Angina pectoris	Y	Excluded from MACE	Atrial fibrillation	Drug eluting stent placement to Circumflex	N (stopped temporarily)	235	Diabetes, erectile dysfunction, hypercholesterolemia	rosuvastatin, colesevelam HCl, glimepiride, metformin
	7 NB-304	62/F	CVA	Y	Broad, Custom	None	None	Y	90	Diabetes, hypercholesterolemia	lisinopril, lovastatin, nicotinic acid, lipitac, glipizide

Table 37 Patients Experiencing Major CV Events and/or Revascularization in the NB Clinical Development Program (*Continued*)

Treatment Group	Patient ID/ Study	Age (yrs)/ Sex	Adverse Event (MedDRA Preferred Term)	SAE	MACE category	Other CV AEs (MedDRA Preferred Term)	Intervention	Discontinued Study Drug	Study Day of AE Onset	Selected Comorbidities and Risk Factors	Selected Concomitant Medications
Post-treatment events											
NB16 (N=633)	8 NB-301	50/M	Acute MI	Y	NA	None	Stent in RCA	NA	discontinued on D13 for GERD; MI on D49	GERD, hypertension, hyperglycemia, hyperlipidemia	acetylsalicylic acid, atorvastatin, fenofibrate, fish oil, ranitidine hydrochloride

a. Femoral artery stenosis was a complication resulting from cardiac catheterization.
b. This patient had a concurrent SAE of chest pain.
Table includes all Custom MACE and revascularization events. NB Clinical Development Program: 1515 Placebo patients, 3239 NB patients
Abbreviations: AE= adverse event; CV=cardiovascular; CVA=cerebrovascular accident; GERD=gastroesophageal reflux disease; HCl=hydrochloride; HDL=high-density lipoprotein; LAD=left anterior descending (artery); MACE=major adverse cardiovascular event; MedDRA=Medical Dictionary for Regulatory Activities; MI=myocardial infarction; NA=not applicable; RCA=right coronary artery; SAE=serious adverse event.

7.6.2.1.1 Narratives of Treatment-emergent Major CV events

Patient 1 (065-NB-303-048)
NB32 Treatment Group
Myocardial Infarction (non-fatal)

Patient 065-NB-303-048, a 50-year-old White female in the NB32 group, had a relevant medical history of active coronary artery disease, angina pectoris, hyperlipidemia, hypertension, and hypertriglyceridemia and was a current smoker. The patient was receiving the following relevant concurrent medications: acetylsalicylic acid and lisinopril. The patient had a baseline heart rate and blood pressure of 87 bpm and 119/79 mm Hg, respectively. During the study, the patient had blood pressure measurements of 126/79 mm Hg (Week 4) and 121/77 mm Hg (Week 8). Both the patient's screening and Week 4 (Day 29) ECGs were normal. On Day 85 the patient came to the study site for the Week 12 visit and reported chest discomfort which she attributed to heartburn for the past 3 days with increasing frequency and discomfort. Her blood pressure and heart rate were 127/80 mm Hg and 90 bpm, respectively. The chest discomfort, which was substernal and epigastric, had become quite painful and she had began experiencing the burning sensation nearly every hour. ECGs revealed terminal T wave inversions in the precordial leads. The troponin level was mildly elevated. The patient was admitted to the hospital with acute myocardial infarction. Cardiac catheterization revealed stenosis of the left anterior descending coronary artery, which was revascularized with an Endeavor drug eluting stent. The patient was discharged from the hospital on Day 86. The patient discontinued study drug due to the primary reason of myocardial infarction. At the early termination visit, the patient's ECG was normal and her blood pressure was 130/82 mm Hg.

Patient 2 (060-NB-304-016)
NB32 Treatment Group
Myocardial Infarction (non-fatal)

Patient 060-NB-304-016, a 44-year-old White male in the NB32 group, had a relevant medical history of type 2 diabetes mellitus and hyperlipidaemia and was receiving the following concurrent medications: glipizide, metformin, pioglitazone, pravastatin, and fenofibrate. The patient quit smoking about two and a half years ago. The screening ECG was normal. An ECG performed at Week 4 was reported as a change from baseline that was not clinically significant. The clinical assessment was sinus bradycardia. The patient's blood pressure and heart rate were within normal limits on Days 1 (112/77 mm Hg; 77 bpm) and 24 (101/69 mm Hg; 71 bpm), and 52 (101/61 mm Hg; 76 bpm). On Day 55, the patient experienced dizziness, nausea, and hyperhidrosis, which resolved on Day 56. An ECG done by his primary care physician on Day 57 revealed normal sinus rhythm, mild ST segment elevation in lead 3 only and mild ST segment depression in leads V2 to V6, which were new changes from prior ECGs. The patient reported left axillary pain radiating down the left arm since Day 56. The diagnosis was a non ST elevation myocardial infarction with ongoing electrocardiogram changes. It was felt that the myocardial infarction most likely occurred within the 2 days prior to admission. In the emergency room, the patient's blood pressure was 119/79 mm Hg and the heart rate was 79 bpm. CPK, CK-MB, CK-MB index and troponin I results were consistent with acute coronary syndrome. The patient was admitted on Day 57 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 patient had an echocardiogram and Doppler, which showed a mildly dilated left ventricle, mildly decreased left ventricular function, and an estimated left ventricular ejection fraction of 45-50%. The left ventricular inferior wall was severely hypokinetic. The patient was discharged from the hospital on Day 59. The patient discontinued the study and the date of last confirmed dose is Day 57.

Patient 3 (099-NB-301-003)
NB32 Treatment Group
Myocardial Infarction (fatal)

Patient 099-NB-301-003, a 65-year-old White male patient in the NB32 group, died of a severe myocardial infarction on Day 324 of the study. The patient had a relevant medical history of hypertension, hypercholesterolaemia, idiopathic bradycardia, and was receiving the following relevant concurrent medications: lisinopril, lovastatin, acetylsalicylic acid, ibuprofen, and naproxen sodium. At baseline, the patient's screening ECG was abnormal, not clinically significant, with sinus bradycardia with sinus arrhythmia; borderline primary AV block (PR interval = 200 msec). Intermittently during the study, the patient'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 patient remained bradycardic throughout the study, with heart rate ranging from 41 – 57 bpm. Shortly after an unremarkable study visit on Day 312 (Week 44), the patient's wife informed the study site that the patient had experienced chest pain, and that he had made an appointment to see his primary care physician. On Day 324, the patient experienced a sudden death, which was attributed to a myocardial infarction by the investigator, during the camping trip at a remote location. Per the medical examiner narrative, the manner of death was ruled as natural and the cause of death was noted as athlerosclerotic coronary artery disease. No autopsy was performed. The last dose of study drug was on Day 324. The event of myocardial infarction was classified as severe and serious and judged by the investigator to be unlikely related to study drug. No additional cardiovascular-related TEAEs were recorded. No treatment-emergent, clinically significant ECG changes from baseline were recorded during the study.

Patient 7 (075-NB-304-017)
Placebo Treatment Group
Cerebrovascular Accident (non-fatal)

Patient 075-NB-304-017, a 62-year-old White female in the placebo group, had a relevant medical history of type 2 diabetes mellitus and hypercholesterolaemia. Per the hospital report, the patient also has a history of hypertension that was not captured in the patient's medical history for this study. Relevant concomitant medications included lisinopril, lovastatin, nicotinic acid, lipitac, and glipizide. The patient's blood pressure baseline value was 129/85 mm Hg, with values of 134/89 mm Hg at Week 4, 116/79 mm Hg at Week 8, and 108/59 mm Hg at Week 12. On Day 90, the patient experienced a cerebrovascular accident. The patient went to the emergency room complaining of a coordination deficit, weakness in the left leg, and difficulty walking. The patient later noted onset of more pronounced

numbness and weakness of the left upper extremity. In the emergency room, blood pressure was 141/82 mm Hg and the heart rate was 81 bpm. Neurologic exam revealed a deficit of cranial nerve VII with a left facial droop, 3/5 strength in left upper and lower extremities, and decreased left deep tendon reflexes. MRI revealed a focal ischemic injury of the right insula, and MRA of the head and neck was normal. The left lower extremity weakness improved. The patient was discharged on Day 92 with instructions to follow-up with the neurology clinic. The cerebrovascular accident was resolved on Day 90. The patient discontinued study drug due to this event, and the date of the last confirmed dose of study drug is Day 89.

7.6.2.1.2 Narrative of Posttreatment Major CV event

Patient 8 (086-NB-301-040)
Myocardial Infarction (non-fatal)

An additional event of myocardial infarction occurred posttreatment in Patient 086-NB-301-040, a 50-year-old White male in the NB16 group, with a relevant medical history of gastrooesophageal reflux disease, hyperglycemia, hyperlipidaemia, and hypertension. Relevant concomitant medications included acetylsalicylic acid, atorvastatin calcium, fenofibrate, fish oil, and ranitidine hydrochloride. At baseline (Day 1) the patient's heart rate and blood pressure were 69 bpm and 115/77 mm Hg, respectively. On Day 8, the patient experienced worsening gastrooesophageal reflux disease and nausea, for which the patient discontinued study drug. The last confirmed dose of study drug was received on Day 13. The last recorded heart rate and blood pressure at the patient's early termination visit on Day 29 was 63 bpm and 112/73 mm Hg. On Day 49, the patient experienced acute myocardial infarction. He presented to the emergency room on Day 49 with complaints of chest pain that started the previous evening and persisted throughout the day at a milder level; his troponin was found to be elevated (value not specified) and the ECG noted sinus rhythm with borderline ST segment depressions laterally. The patient was treated with aspirin, nitroglycerin, and morphine. A repeat ECG noted sinus bradycardia (heart rate of 46) and T-wave inversions laterally. The patient's blood pressure was stable at around 105 mm Hg systolic, but the heart rate never increased above 75 bpm and generally remained in the low 60s. The patient was treated on Days 50-51 prophylactically with eptifibatide and enoxaparin sodium prior to cardiac catheterization. The right coronary artery was totally occluded in the proximal segment. Mild coronary artery disease of the left anterior descending artery was noted, with approximately 20%-40% stenosis. The main left anterior descending artery was free of disease to the apex. The patient's left ventricular pressure at the time of catheterization was 120/60 mm Hg. A stent was placed in the right coronary artery. The patient began clopidogrel on Day 51. The event of myocardial infarction resolved on Day 52. Due to the patient's limited exposure to NB and the elapsed time since his last dose, it is unlikely that this event is related to study drug.

7.6.2.2 Congestive Heart Failure

Congestive heart failure (including preferred terms of cardiac failure, ejection fraction decreased, dyspnea, exertional dyspnea, pulmonary congestion, cardiomegaly, pericardial effusion) was rare in the NB clinical program (0.7% NB, 0.9% placebo) and few patients discontinued due to potential CHF events (0.2% NB, <0.1% placebo). No patient experiencing congestive heart failure or potential CHF experienced a Major CV event.

7.6.2.3 CV Events in Patients with a History of CV Disease

Patients with a medical history of CV disease at baseline (28.7% Total NB; 28.8% placebo) more frequently experienced CV events (major CV events, atherosclerotic disease, arrhythmias, and congestive heart failure) during the study compared with patients who had no prior CV medical history (CV History: 9.8% Total NB and 10.3% placebo; No CV History: 7.4% Total NB and 6.5% placebo). In general, the pattern, incidence, and comparison between treatment groups of CV AEs among patients with CV medical history were similar to that of the Primary Dataset.

7.6.3 Psychiatric-Related Events

The psychiatric special topic consisted of preferred terms for the TME subclasses of depression, suicide/self-injury, anxiety, and sleep disorders (see Appendix 7, Table 65). This topic is of special interest because psychiatric events have been observed with centrally-acting obesity agents as well as antidepressants (including bupropion).

Overall, psychiatric events were more common in the Total NB group than in the placebo group (17% and 13%, respectively; Table 38). These events occurred predominantly in the sleep disorders and anxiety subclasses in both the Total NB and placebo groups. Only one psychiatric-related SAE was reported, a single event of anxiety (described in Section 7.6.3.3). Discontinuations due to psychiatric events were infrequent and similar across treatment groups.

Table 38 Incidence of Treatment-Emergent Adverse Events for TME of Psychiatric Events: Primary Dataset, Double-Blind Treatment Phase

Psychiatric TME Subclass	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Patients with any Psychiatric TME AE	**196 (12.9%)**	**86 (13.6%)**	**449 (17.6%)**	**541 (16.7%)**
Depression	52 (3.4%)	15 (2.4%)	75 (2.9%)	91 (2.8%)
Suicide/Self-injury[a]	3 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Sleep Disorders	107 (7.1%)	56 (8.8%)	290 (11.4%)	349 (10.8%)
Anxiety	67 (4.4%)	22 (3.5%)	168 (6.6%)	195 (6.0%)
Patients with any Psychiatric TME treatment-emergent SAE	**0**	**0**	**1 (<0.1%)**	**1 (<0.1%)**
Anxiety	0	0	1 (<0.1%)	1 (<0.1%)
Patients discontinued due to a Psychiatric TME AE	**40 (2.6%)**	**16 (2.5%)**	**71 (2.8%)**	**91 (2.8%)**
Depression	18 (1.2%)	8 (1.3%)	22 (0.9%)	30 (0.9%)
Suicide/Self-injury[a]	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Sleep Disorders	8 (0.5%)	7 (1.1%)	23 (0.9%)	31 (1.0%)
Anxiety	13 (0.9%)	2 (0.3%)	25 (1.0%)	30 (0.9%)

a. The only preferred term that occurred in this category was suicidal ideation.
A list of preferred terms defining the TME for psychiatric events can be found in Appendix 7, Table 65.
Abbreviations: AE=adverse event; SAE=serious adverse event; TME=targeted medical event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

7.6.3.1 Depression

Depression was of special interest because of historical concerns surrounding both obesity and antidepressant treatment in relation to suicidality. A boxed warning is required by the FDA in the prescribing information for all antidepressant drugs marketed in the U.S. An association between depression and obesity has been well-established in clinical studies (Gariepy et al., 2010; Deshmukh and Franco, 2003; Vanina et al., 2002) and an epidemiological study (Petry et al., 2008). In a study of approximately 41,654 patients, a statistically significant association was observed between BMI 30 to 39.9 kg/m^2 and 40+ kg/m^2 and risk of depression, with odds ratios of 1.53 (1.41-1.67) and 2.02 (1.74-2.35), respectively for the two BMI categories. There was a roughly 3% to 5% increased risk of depression for each unit increase in BMI (Petry et al., 2008).

Risk of depression was assessed in multiple ways throughout the NB clinical program, including AEs, Columbia Classification Algorithm of Suicide Assessment (C-CASA), IDS-SR, and an open-label study in depressed patients. A thorough review of this data revealed no increased risk of depression or suicidality with NB treatment. It should be noted that with the exception of one small study (NB-402, N=25) specifically designed to evaluate obese/overweight and depressed patients, patients who met the IDS-SR criteria for depressive symptoms (see Section 7.6.3.1.1) were not enrolled in NB clinical studies. Of note, 10.9% of patients in the Total NB group and 12.7% of patients in the placebo group had a history of depression.

Events related to depression occurred less frequently in NB-treated patients than placebo patients (2.8% vs. 3.4%) and discontinuations due to depression-type AEs were also less frequent in the Total NB group (0.9%) compared with placebo (1.2%). A detailed discussion of the assessment of depression and related events in the NB program is provided below.

Table 39 Incidence of Treatment-Emergent Adverse Events for TME Subclass of Depression: 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 (%)
Patients with any Depression AE	**52 (3.4%)**	**15 (2.4%)**	**75 (2.9%)**	**91 (2.8%)**
Depression	23 (1.5%)	9 (1.4%)	24 (0.9%)	34 (1.0%)
Depressed mood	18 (1.2%)	2 (0.3%)	23 (0.9%)	25 (0.8%)
Affect lability	3 (0.2%)	1 (0.2%)	7 (0.3%)	8 (0.2%)
Mood altered	2 (0.1%)	0	7 (0.3%)	7 (0.2%)
Mood swings	1 (<0.1%)	1 (0.2%)	6 (0.2%)	7 (0.2%)
Tearfulness	1 (<0.1%)	0	5 (0.2%)	5 (0.2%)
Apathy	3 (0.2%)	0	3 (0.1%)	3 (<0.1%)
Crying	1 (<0.1%)	0	2 (<0.1%)	2 (<0.1%)
Depressive symptom	2 (0.1%)	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Anhedonia	1 (<0.1%)	0	0	1 (<0.1%)
Dysthymic disorder	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Emotional distress	0	0	1 (<0.1%)	1 (<0.1%)
Major depression	1 (<0.1%)	1 (0.2%)	0	1 (<0.1%)
Negative thoughts	1 (<0.1%)	0	0	0
Patients with any treatment-emergent Depression SAE	**0**	**0**	**0**	**0**
Patients discontinued due to any Depression AE	**18 (1.2%)**	**8 (1.3%)**	**22 (0.9%)**	**30 (0.9%)**
Depression	13 (0.9%)	6 (0.9%)	10 (0.4%)	16 (0.5%)
Depressed mood	4 (0.3%)	0	4 (0.2%)	4 (0.1%)
Affect lability	0	0	4 (0.2%)	4 (0.1%)
Mood swings	1 (<0.1%)	1 (0.2%)	1 (<0.1%)	2 (<0.1%)
Tearfulness	0	0	1 (<0.1%)	1 (<0.1%)
Apathy	0	0	1 (<0.1%)	1 (<0.1%)
Emotional distress	0	0	1 (<0.1%)	1 (<0.1%)
Major depression	0	1 (0.2%)	0	1 (<0.1%)

A list of preferred terms defining the depression TME can be found in Appendix 7, Table 65. Abbreviations: AE=adverse event; SAE=serious adverse event; TME=targeted medical event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

7.6.3.1.1 Inventory of Depressive Symptomatology-Self-Reported Scores in Phase 3 Studies

During the Phase 3 studies, changes in mood or depressive symptoms were routinely monitored using the self-administered 30-item Inventory of Depressive Symptomatology-Self-Reported (IDS-SR) questionnaire (Rush et al., 1996). The IDS-SR is scored from 0-84 (www.ids-qids.org):

0-13 = no depression
14-25 = mild depression
26-38 = moderate depression
39-48 = moderate to severe depression
≥49 = very severe depression

Individual items were scored using a 4-point scale of 0 to 3, with 0 being the least severe and 3 being the most severe. A higher score is indicative of more severe depressive symptoms.

At baseline, patients were required to have an IDS-SR total score <30 and scores <2 on items 5 (sadness), 6 (irritability), 7 (anxiety/tension) and 18 (thoughts of death or suicidality). Mean baseline IDS-SR total scores were approximately 7 across all Phase 3 studies, indicating a patient population generally free of depressive symptoms. Based on the integrated IDS-SR results, there did not appear to be any increased risk of changes in mood or the development of depressive symptoms following NB treatment with respect to the total IDS-SR score as well as based on Items 5, 6, 7, and 18 (feeling sad, irritable, anxious or tense, or thoughts of death or suicide, respectively). Although a small difference in the total score was observed between NB- and placebo-treated patients, this was primarily due to a treatment effect for items measuring appetite, weight, gastrointestinal symptoms, and other somatic symptoms. Of note, review of the 12 NB cases where item 18 was scored ≥2 showed that only one case was indicative of actual suicidal ideation, as opposed to non-specific thoughts of death (Section 7.6.3.1.3).

Table 40 Treatment-emergent IDS-SR Item Scores; Safety Analysis Set, Double-Blind Treatment Phase, Combined Phase 3 Studies

Item Score	Placebo N=1430 n (%)	Total NB N=3051 n (%)
At least 1 post-baseline score ≥2:		
Sadness (Item 5)	45 (3.4%)	93 (3.5%)
Irritability (Item 6)	46 (3.4%)	107 (4.0%)
Anxiety/Tension (Item 7)	64 (4.8%)	167 (6.3%)
Thoughts of Death or Suicidality (Item 18)	5 (0.4%)	12 (0.5%)
At least 1 post-baseline Total score ≥25	55 (4.1%)	123 (4.6%)

Abbreviations: IDS-SR= Inventory of Depressive Symptomatology - Self-Reported; Total NB=all doses of combination naltrexone and bupropion treatment.

7.6.3.1.2 Depression Data from Other Studies

The Phase 2 Studies OT-101 and NB-201 used measures other than the IDS-SR to assess depression, including the Hospital Anxiety and Depression Scale (HADS), the suicidal ideation question of the Mood Assessment Questionnaire, and the Maier subscale of the 17-item Hamilton Depression Scale. Across these two studies, there was no evidence that NB increased the incidence of anxiety, depression, or suicidal ideation.

There were two additional small, open-label Phase 2 studies: One was conducted in overweight or obese patients with nicotine dependence (Study NB-401, N=30) and the other in overweight or obese patients with major depression (Study NB-402, N=25). In Study NB-401, baseline mean IDS-SR scores were low and remained in the non-depressed range throughout the study. During the study one elevated IDS-SR score of sadness and another for anxiety/tension were reported; psychiatric AEs led to study discontinuation for one patient with insomnia. In Study NB-402, patients were depressed and had elevated IDS-SR

scores at baseline. Mean IDS-SR scores were decreased throughout the study indicating improvement in depressive symptoms. Psychiatric AEs most commonly involved insomnia, abnormal dreams, or irritability; three patients discontinued due to psychiatric events (one each with insomnia, irritability and mood swings). The small sample size, alternative patient selection criteria, and open-label design of these two studies present limitations to the interpretation of the results; overall the pattern of AEs observed was consistent with that observed in the Phase 3 program and there was no evidence of treatment-emergent suicidality in either study.

7.6.3.1.3 Suicidality

Concerns over possible increased risk of suicidality with antidepressant drug use has led to heightened vigilance with respect to suicidal risk assessment for centrally-acting drugs in clinical development across a broad range of therapeutic areas.

In agreement with the FDA, the C-CASA, a retrospective assessment tool of suicidality, was used to assess AEs that could represent suicidal events (behavior and ideation). Analysis of C-CASA data was performed by an independent group blinded to treatment assignment. The results of the C-CASA analyses for the five placebo-controlled clinical trials in the Primary Dataset were pooled and are summarized below.

The primary endpoint of this meta-analysis was suicidal ideation or worse (Codes 1, 2, 3, or 4 combined, as described in Table 41), also called suicidality or suicidal behavior and ideation, based upon the C-CASA categorization. There were no completed suicides, suicide attempts, or preparatory acts towards imminent suicidal behavior in any treatment group. The incidence of suicidality (Codes 1, 2, 3, and 4 combined) was one patient (<0.1%) in the Total NB group compared with three patients (0.2%) in the placebo group with an overall odds ratio for suicidal ideation or worse of 0.14 (95% confidence interval [CI]: 0.00, 1.72) for Total NB compared with placebo, suggesting there is no treatment difference for suicidal behavior.

Table 41 Incidence Rates for C-CASA Suicidality Outcome Codes by Treatment; Primary Dataset, Double-Blind Treatment Phase

C-CASA Classification	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
No Event (Code 0)	1444 (95.3)	3075 (94.9)
Completed Suicide (Code 1)	0 (0.0)	0 (0.0)
Suicide Attempt (Code 2)	0 (0.0)	0 (0.0)
Preparatory Acts Toward Imminent Suicidal Behavior (Code 3)	0 (0.0)	0 (0.0)
Suicidal Ideation (Code 4)	3 (0.2)	1 (<0.1)
Self-Injurious Behavior, Intent Unknown (Code 5)	0 (0.0)	0 (0.0)
Not Enough Information, Fatal (Code 6)	0 (0.0)	0 (0.0)
Other [No evidence of suicidality or deliberate self-harm] (Code 8)	68 (4.5)	162 (5.0)
Not Enough Information, Non-Fatal (Code 9)	0 (0.0)	1 (<0.1)

Abbreviations: C-CASA= Columbia Classification Algorithm of Suicide Assessment; Total NB=all doses of combination naltrexone and bupropion treatment.

The secondary endpoint of this meta-analysis was preparatory actions or worse (Codes 1, 2, or 3 combined, also called suicidal behavior). There were no events in this category for any patients during these studies.

In summary, the results of the suicidality meta-analysis and the IDS-SR scores suggest that the administration of NB as a weight loss agent does not increase suicidal ideation or behavior in obese/overweight patients.

7.6.3.2 Sleep Disorders

Events of sleep disorder were more frequently reported in NB-treated patients than placebo-treated patients (Table 42). This was primarily due to insomnia, which is a common side effect of bupropion monotherapy and was the most frequent sleep disorder event reported. Insomnia was more common in NB- than placebo-treated patients (8.6% vs. 5.9%) and tended to occur primarily during the dose-escalation phase in NB patients. Events of insomnia were rarely severe (0.4% Total NB, <0.1% placebo) and discontinuations were infrequent and similar across treatment groups (0.7% Total NB, 0.5% Placebo). The use of sedative/hypnotics was similar across treatment groups (13.5% Total NB, 13.8% placebo). Somnolence was infrequently reported and rarely led to discontinuation.

Table 42 Incidence of Treatment-Emergent Adverse Events for TME Subclass of Sleep Disorders: 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 (%)
Patients with any Sleep Disorder AE	**107 (7.1%)**	**56 (8.8%)**	**290 (11.4%)**	**349 (10.8%)**
Insomnia	89 (5.9%)	42 (6.6%)	233 (9.2%)	277 (8.6%)
Somnolence	12 (0.8%)	9 (1.4%)	32 (1.3%)	42 (1.3%)
Middle insomnia	3 (0.2%)	1 (0.2%)	16 (0.6%)	17 (0.5%)
Poor quality sleep	2 (0.1%)	1 (0.2%)	8 (0.3%)	9 (0.3%)
Initial insomnia	4 (0.3%)	2 (0.3%)	6 (0.2%)	8 (0.2%)
Hypersomnia	0	1 (0.2%)	0	1 (<0.1%)
Patients with any Sleep Disorder SAE	**0**	**0**	**0**	**0**
Patients discontinued due to any Sleep Disorder AE	**8 (0.5%)**	**7 (1.1%)**	**23 (0.9%)**	**31 (1.0%)**
Insomnia	7 (0.5%)	5 (0.8%)	17 (0.7%)	23 (0.7%)
Somnolence	0	1 (0.2)	6 (0.2%)	7 (0.2%)
Poor quality sleep	1 (<0.1%)	0	0	0
Hypersomnia	0	1 (0.2%)	0	1 (<0.1%)

A list of preferred terms defining the Sleep Disorders TME can be found in Appendix 7, Table 65. Abbreviations: AE=adverse event; SAE=serious adverse event; TME=targeted medical event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

7.6.3.3 Anxiety

Anxiety, another common AE associated with bupropion monotherapy, occurred more frequently in the Total NB group compared with placebo (Table 43) and was rarely severe (0.3% NB32 vs. 0% placebo). Discontinuations due to any AE in the anxiety TME subclass were infrequent (<1% in each group). Patients with a history of anxiety or depression had a

higher incidence of anxiety-type events than patients without a history of anxiety or depression.

One NB-treated patient experienced a serious event of anxiety, a 56-year-old Black female with an active history of asthma. Relevant concomitant medication included albuterol inhaler, 90 mcg/puff (2 puffs every 4 hours as needed) and Flovent. On Day 18 (9 February 2008), the patient began to experience dyspnea on exertion when climbing stairs that did not respond to her asthma medications. She also experienced anxiety and palpitations on Day 18. She attributed these symptoms to study drug and stopped treatment on Day 21; she presented to the emergency room on Day 22 and was hospitalized with anxiety accompanied by dyspnea on exertion, angina pectoris and palpitations. Outpatient medications were continued along with nebulizer treatments. Her cardiac workup was negative with exception of a small area of reversible inferolateral ischemia on a stress test. She was treated in the hospital on Day 23 with metoprolol for an event of supraventricular tachycardia and discharged on Day 24 with resolution of all her presenting symptoms. She discontinued study drug due to the primary event of dyspnea on exertion. It is possible that these events are related to the asthma-related sympathomimetic use rather than to NB treatment.

Table 43 Incidence of Treatment-Emergent Adverse Events for TME Subclass of Anxiety: 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 (%)
Patients with any Anxiety AE	**67 (4.4%)**	**22 (3.5%)**	**168 (6.6%)**	**195 (6.0%)**
Anxiety	43 (2.8%)	16 (2.5%)	108 (4.2%)	127 (3.9%)
Irritability	28 (1.8%)	6 (0.9%)	66 (2.6%)	74 (2.3%)
Agitation	1 (<0.1%)	0	8 (0.3%)	8 (0.2%)
Patients with any Anxiety SAE	**0**	**0**	**1 (<0.1%)**	**1 (<0.1%)**
Anxiety	0	0	1 (<0.1%)	1 (<0.1%)
Patients Discontinued due to any Anxiety AE	**13 (0.9%)**	**2 (0.3%)**	**25 (1.0%)**	**30 (0.9%)**
Anxiety	10 (0.7%)	1 (0.2%)	19 (0.7%)	21 (0.6%)
Irritability	3 (0.2%)	1 (0.2%)	4 (0.2%)	7 (0.2%)
Agitation	0	0	2 (<0.1%)	2 (<0.1%)

A list of preferred terms defining the Anxiety TME can be found in Appendix 7, Table 65. Abbreviations: AE=adverse event; SAE=serious adverse event; TME=targeted medical event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

7.6.3.4 Psychosis and Psychotic Disorders

Psychosis preferred terms weren't included in the Psychiatric TME, therefore, these events were evaluated separately. The incidence of Psychosis and Psychotic Disorders SMQ events were similar between the Total NB group (0.7%) and the placebo group (0.5%). There were no SAEs reported and few patients discontinued due to a Psychosis and Psychotic Disorders SMQ events 0.2% Total NB; 0% placebo).

None of the patients with potential psychotic symptoms experienced frank psychosis. In the Total NB group, 2 patients (<0.1%) reported hallucination: One appeared associated with hypoglycemic episodes and the other was sleep-onset hallucinations associated with

nightmares; both patients were discontinued from the study with prompt event resolution. A third patient receiving NB32 reported a feeling of paranoia (verbatim term) for a single day on Day 15 and remained in the study until Day 267 when she was discontinued for inattentiveness. No patients in the placebo group reported either of these events.

7.6.4 Cognitive

Cognitive disorders are of special interest because centrally-acting agents have been shown to impact aspects of cognition. The cognitive disorder TME consisted of preferred terms for the subclasses of attention, other cognitive NOS, memory impairment, and language (see Appendix 7, Table 67).

While cognitive events were infrequent, there was a greater incidence of cognitive disorder events in NB-treated patients than placebo-treated patients (2.9% and 1.0%, respectively; Table 44). There were no SAEs, severe events were uncommon and occurred at a similar frequency between Total NB and placebo groups, and few patients in either treatment group discontinued due to cognitive disorder events.

Table 44 Incidence of Treatment-Emergent Adverse Events for Cognitive Disorders TME subclasses: Primary Dataset, Double-Blind Treatment Phase

Cognitive Disorders TME Subclasses	Placebo (N=1515) n (%)	NB16 (N=633) n (%)	NB32 (N=2545) n (%)	Total NB (N=3239) n (%)
Patients with any AE	**15 (1.0%)**	**10 (1.6%)**	**83 (3.3%)**	**94 (2.9%)**
Attention	5 (0.3%)	6 (0.9%)	39 (1.5%)	45 (1.4%)
Other cognitive NOS	7 (0.5%)	2 (0.3%)	30 (1.2%)	32 (1.0%)
Memory impairment	5 (0.3%)	3 (0.5%)	20 (0.8%)	24 (0.7%)
Language	0	0	1 (<0.1%)	1 (<0.1%)
Patients with any treatment-emergent SAE	**0**	**0**	**0**	**0**
Patients discontinued due to AE	**4 (0.3%)**	**3 (0.5%)**	**24 (0.9%)**	**27 (0.8%)**
Attention	1 (<0.1%)	2 (0.3%)	11 (0.4%)	13 (0.4%)
Other cognitive NOS	3 (0.2%)	0	11 (0.4%)	11 (0.3%)
Memory impairment	0	1 (0.2%)	2 (<0.1%)	3 (<0.1%)

A list of MedDRA preferred terms associated with each subclass can be found in see Appendix 7, Table 67.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

7.6.5 Seizures and Convulsions

Two patients (<0.1%) in the NB development program each experienced a single seizure event and both had received NB32 treatment. Neither patient had a prior history of seizure. One patient had diabetes with a history of hypoglycemia, and event details are suggestive of, but not conclusive for, hypoglycemic seizure. Both events were serious and led to study discontinuation. Both patients recovered without further event. Brief narratives of these two events are provided in Section 7.6.5.1. One additional NB32 patient who lost consciousness at their workplace was diagnosed by emergency room personnel as having a syncopal episode resulting from Valsalva maneuver upon exertion. The clinical presentation included

some symptoms that could also suggest a convulsive episode (limb movements and foaming of the mouth). The patient discontinued study drug due to this episode.

Data from bupropion product labeling and the literature indicate that bupropion is associated with a dose-related risk of seizures. Bupropion doses up to 300 mg/day have been associated with a seizure rate of approximately 0.1% (Dunner et al., 1998), while doses up to 450 mg/day of the immediate release formulation are associated with a rate of approximately 0.4% (Johnston et al., 1991). Consistent with bupropion doses of 300 mg/day, the rate of seizure in the NB program was <0.1% and the two cases of seizures were single events that resolved without sequelae.

7.6.5.1 Brief Narratives of Seizure Events

Patient 066-NB-303-016, a 40-year-old White female, was randomized to the NB32 group. She had no prior history of convulsion or seizure disorder. At the time of the event, the patient was receiving the following concurrent medications: Eugynon and polycarbophil calcium. On Day 144, the patient 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 patient 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 patient 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 patient 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 patient reported having an episode of presyncope (Days 148-193) and syncope (Days 150-159). These events were unwitnessed. The patient was seen by a neurologist on Day 191 who recommended no anti-seizure medication and follow-up in 3 months. The patient did not complete study drug due to the event of convulsion and discontinued from the study on Day 195. The patient subsequently reported that there were no more seizures since the original one reported.

Patient 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 patient had one prior AE of hypoglycemia on Day 38. On Day 110, while shopping, the patient's daughter noticed that the patient was pale. The daughter thought the patient was hypoglycemic and gave the patient chocolate. The patient 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 patient regained consciousness about 7 to 10 minutes later with no recollection of the episode. EMS tested the patient's blood sugar which was initially 74 and subsequently rose to 85 and then to the 90s on two other checks. Per the patient, the seizure was preceded by two hot flashes and a feeling of lightheadedness. Neurological examination was normal. During admission, no arrhythmias on telemetry were noted and a myocardial infarction was ruled out. A CT scan, MRI, and EEG were normal.

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 patient 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 patient discontinued the study on Day 141 due to a grand mal convulsion. A follow-up neurological and physical exam were both normal, and the patient has remained seizure free for a total of 6 months.

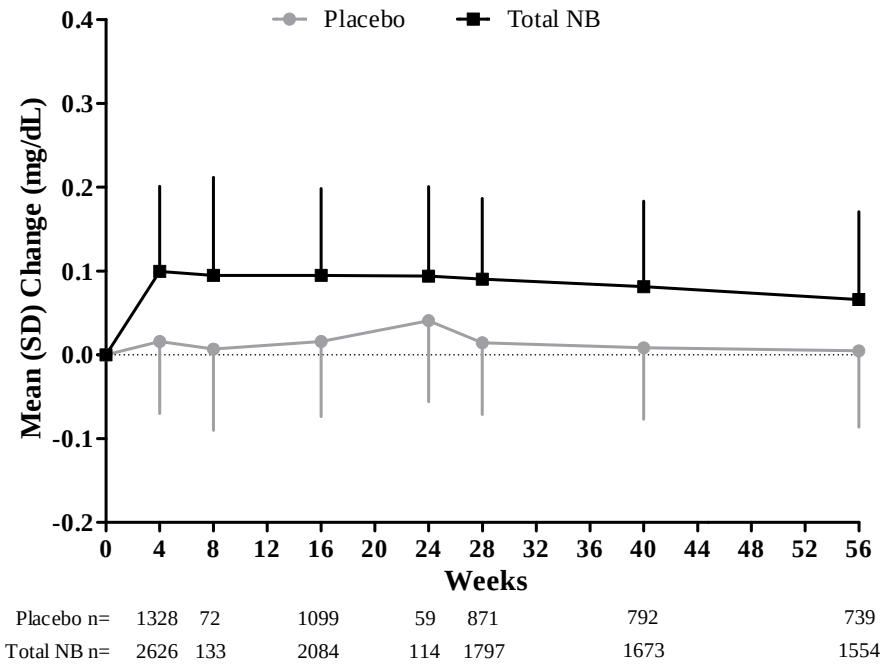
7.6.6 Renal Function

The special topic of renal function was addressed to further evaluate observations of a small increase in serum creatinine observed with NB treatment in the Phase 3 studies, as described below. The likely reason for the creatinine increases is the finding that bupropion and its metabolites competitively inhibit the OCT2 in the basolateral membrane of the renal tubule responsible for creatinine secretion. Therefore, the small increases in creatinine do not appear to be the result of change in glomerular filtration. Clinical findings on creatinine and blood urea nitrogen (BUN) are described below followed by AEs related to renal function.

7.6.6.1 Renal Function Laboratory Findings

Increases in mean serum creatinine in the Total NB group were larger compared with the placebo group throughout treatment (Figure 35). Creatinine values were highest at Week 4, with changes from baseline in mean serum creatinine of 0.10 mg/dL and 0.02 mg/dL for NB- and placebo-treated patients, respectively. The creatinine increase was similar to that observed with bupropion alone in Study NB-201 (mean increase from baseline: 0.12 mg/dL at Week 24). Mean values for the Total NB group remained higher than baseline at endpoint (0.07 mg/dL); however, they were decreased relative to Week 4, indicating that the changes were not progressive. For NB-treated patients who had a post baseline value above the upper limit of normal (ULN), mean creatinine values were highest at Week 4 and declined somewhat thereafter, suggesting that even in the patients with the highest creatinine values, the change was not progressive, and tended to reverse over time.

Figure 35 Creatinine, Mean change from Baseline by Visit: Primary Dataset, Double-Blind Treatment Phase



Results are based on observed values.
Abbreviations: SD=standard deviation; Total NB=all doses of combination naltrexone and bupropion treatment.

There was a low correlation (R^2 <0.2) between increases in creatinine and baseline creatinine. Patients with somewhat lower baseline renal function do not appear to be at any higher risk for increased creatinine while taking NB. Likewise, there was no meaningful correlation between increases in creatinine and BUN, weight loss, SBP, or DBP.

Patients in both treatment groups generally had normal creatinine at baseline. Shifts to high creatinine (>ULN; 1.20 mg/dL for females and 1.30 mg/dL for males) at any post baseline assessment occurred at a higher incidence in the Total NB group (7.6%) compared with the placebo group (1.9%). In patients with diabetes, the incidence of a shift to high creatinine levels in the NB32 and placebo groups (12.7% and 3.1%, respectively) was greater than in patients without diabetes (7.5% and 1.7%, respectively). A greater proportion of NB-treated patients had creatinine values of special interest (defined in Table 45) compared with placebo-treated patients; although the incidence was less than 1.0% in either treatment group. Two (<0.1%) of 3239 patients in the Total NB group compared with 0 of 1515 patients in the placebo group had a single creatinine measurement >2.0 mg/dL, both of which were reported as an AE. Creatinine values for both patients returned to values within the normal range while continuing study drug.

Table 45 Incidence of Post-Baseline Creatinine Values of Special Interest: Primary Dataset, Double-Blind Treatment Phase

Post-baseline change in creatinine	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
≥50% increase from baseline and >ULN	2 (0.13%)	18 (0.56%)
≥100% increase from baseline	0	2 (0.06%)
>2 mg/dL, if baseline ≤2 mg/dL	0	2 (0.06%)

To meet criteria for creatinine value of special interest, post-baseline value had to be more extreme than the baseline value.
Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment; ULN=upper limit of normal.

For BUN, there were no differences between the Total NB and placebo groups in mean changes from baseline to endpoint (0.02 and 0.08 mg/dL, respectively) and from baseline to maximum (1.75 and 1.95 mg/dL, respectively) as well as in shifts to high BUN and potentially clinically significant values at any post baseline assessment. The lack of effect on BUN suggests that the small changes in creatinine do not reflect a change in glomerular filtration. As noted earlier, it is more likely that bupropion and its metabolites are competitively inhibiting OCT2 in the basolateral membrane of the renal tubule, which is responsible for creatinine secretion (Section 5.3).

Additionally, elevations in creatinine were not associated with changes in urine protein, erythrocytes, pH, leukocytes or edema, weight gain, or other findings.

7.6.6.2 Renal Function Events

Overall, there was a slightly higher incidence of patients with renal events of special interest in the Total NB group compared with the placebo group (0.65% and 0.20%, respectively; Table 46). There were no SAEs and discontinuations resulting from these AEs were rare (0.06% Total NB, 0.07% placebo). Patients with diabetes reported a higher incidence of renal events compared with patients without diabetes; the incidence was similar between the Total NB and placebo groups (1.20% and 1.18%, respectively).

Of the renal events of interest (see Appendix 7, Table 68), only increased blood creatinine and increased blood urea were reported. Events of increased blood creatinine were reported more frequently in the Total NB group compared with the placebo group (0.52% vs. 0.13%). Increases in creatinine in individual patients were not associated with other AEs. Only two patients discontinued due to either AE, both treated with NB32 who experienced increased blood creatinine. These two patients had normal creatinine at baseline and the values returned to normal after stopping study treatment. Both patients were on concomitant medications for the treatment of hypertension; in addition, one of the two patients treated with NB32 had a history of being treated for rheumatoid arthritis and herpes zoster, while the other patient had a history of being treated for osteoarthritis.

Table 46 Incidence of Renal Treatment-Emergent Adverse Events of Special Interest: Primary Dataset, Double-Blind Treatment Phase

Preferred term	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Patients with any renal AE	**3 (0.20%)**	**21 (0.65%)**
Blood creatinine increased	2 (0.13%)	17 (0.52%)
Blood urea increased	1 (0.07%)	1 (0.03%)
Discontinuation due to renal AEs	**1 (0.07%)**	**2 (0.06%)**
Blood creatinine increased	0	2 (0.06%)
Blood urea increased	0	0

Renal events of interest are defined in Appendix 7, Table 68. Only events that occurred in at least 1 patient are presented.
Abbreviations: AE= adverse event; Total NB=all doses of combination naltrexone and bupropion treatment.

7.6.7 Liver Function and Gallbladder

The Liver and Gallbladder special topic consisted of categories and preferred terms for the subtopics of Potential Hepatotoxicity and Gallbladder (see Appendix 7, Table 69 and Table 70, respectively). This topic was of special interest because of potential hepatotoxicity with naltrexone and the increased incidence of gallbladder disease in females and in patients experiencing rapid weight loss.

7.6.7.1 Potential Hepatotoxicity

Naltrexone prescribing information indicates that naltrexone has the capacity to cause hepatocellular injury when given in high doses (daily doses >300 mg). Hepatotoxicity was not observed in the NB clinical program which utilized maximum daily doses of naltrexone < 50 mg (16 mg, 32 mg, and 48 mg). Hepatic events of interest occurred rarely (<1.0% in either treatment group) and were generally similar between treatment groups. Few patients in either group discontinued due to a hepatic event (Table 47). There were no meaningful differences in the incidence of hepatic events between the Total NB and placebo groups with respect to age, race, obesity class, the occurrence of ALT or AST values >3x ULN during the study, ≥5% weight loss at endpoint, alcohol use, or diabetes history.

Table 47 Incidence of Hepatic Treatment-Emergent Adverse Events of Special Interest: Primary Dataset, Double-Blind Treatment Phase

Preferred term	Placebo (N=1515) n (%)	Total NB (N=3239) n (%)
Patients with any hepatic AE	**16 (1.06%)**	**40 (1.23%)**
ALT increased	7 (0.46%)	18 (0.56%)
AST increased	2 (0.13%)	13 (0.40%)
Blood bilirubin increased	1 (0.07%)	1 (0.03%)
Hepatic enzyme increased	1 (0.07%)	7 (0.22%)
Hepatic function abnormal	1 (0.07%)	4 (0.12%)
Liver function test abnormal	4 (0.26%)	3 (0.09%)
Discontinuation due to hepatic AEs	**2 (0.13%)**	**8 (0.25%)**
ALT increased	1 (0.07%)	2 (0.06%)
AST increased	0	0
Blood bilirubin increased	1 (0.07%)	0
Hepatic enzyme increased	0	4 (0.12%)
Hepatic function abnormal	0	0
Liver function test abnormal	0	1 (0.03%)

Hepatic events of interest are defined in Appendix 7, Table 69. Only events that occurred in at least 1 patient are presented.
Abbreviations: AE= adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; Total NB=all doses of combination naltrexone and bupropion treatment.

Analysis of clinical chemistry parameters related to liver function (ALT, AST, albumin and bilirubin) also showed no apparent differences between patients treated with Total NB or placebo:

- Mean changes from baseline to endpoint were similar between treatment groups for liver function parameters:
    - ALT: -2.02 IU/L Total NB, -1.53 IU/L placebo
    - AST: -1.03 IU/L Total NB, -0.64 IU/L placebo
    - Albumin: 0.03 g/dL Total NB, <0.01 g/dL placebo
    - Bilirubin: 0.02 mg/dL Total NB, 0.03 mg/dL placebo
- No patients met Hy's Law criteria (Hy's Law 1 is defined as ALT >3 x ULN and bilirubin >2 x ULN; Hy's Law 2 is defined as AST >3 x ULN and bilirubin >2 x ULN).
- The proportion of patients having ALT or AST values of interest (>3 x ULN at 2 consecutive visits or >5 x ULN at any post-baseline visit) were low and similar between the Total NB and placebo groups.

7.6.7.2 Gallbladder

Overall, gallbladder events were infrequent and occurred at similar incidences in the Total NB and placebo groups (0.7% and 0.5%, respectively), were rarely serious (0.3% NB, <0.1% placebo) and generally did not lead to discontinuation (<0.1% in both treatment groups). An SAE of cholecystitis was reported in 8 NB patients and 1 placebo patient. These patients all underwent cholecystectomy and all but one in the NB group continued in the study on study medication.

It is known that gallbladder disease occurs more frequently in females than in males, and it is also recognized (National Digestive Diseases Information Clearinghouse, NIDDK, NIH) that cholecystitis is associated with obesity and rapid weight loss. Eight of the nine patients who developed cholecystitis were female. Other than sex, there were no meaningful differences in the incidence of gallbladder events between the Total NB and placebo groups as a function of demographic subgroup, disease history, or concomitant medications.

7.6.8 Additional Safety Topics of Medical Interest

Additional special topics of medical interest that were examined included events of Hypersensitivity Reaction/Skin Rash; Joint and Muscle Pain; and Sexual Dysfunction (see Appendix 7, Table 71, Table 72, and Table 73, respectively). Findings indicated no effect of NB treatment over placebo in any of these categories.

Bupropion is known to be associated with rare reports of anaphylactoid/anaphylactic reactions, erythema multiforme and Stevens-Johnson syndrome, and symptoms which may resemble serum sickness. No events of anaphylaxis and only two events of angioedema were reported in NB-treated patients. There were no reports of erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. No important differences were identified between the treatment groups in the incidence or seriousness of these events, and the percentage of patients who discontinued treatment was also similar across groups.

The incidence of Joint and Muscle Pain events was generally lower in NB-treated patients than in the placebo group. SAEs were rare and there was no difference in the incidence of discontinuations due to AEs across treatments.

The incidence of sexual dysfunction with NB treatment was low and when observed, occurred early in treatment. No SAEs were reported in this special topic and discontinuations were infrequent across treatment groups.

7.7 Other Safety Parameters

7.7.1 Clinical Laboratory Evaluations

A review of clinical laboratory evaluations was conducted for the Primary Dataset and for differences between the Diabetic and Nondiabetic Datasets.

7.7.1.1 Primary Dataset

No meaningful changes in hematology parameters were observed in the NB clinical program. Mean values and mean changes from baseline to endpoint were similar between the Total NB

and placebo groups. Shifts to low hematology values were generally observed with similar frequency in the Total NB and placebo groups. Shifts to high hematology values were observed in <5% of patients for any parameter. The only shifts that occurred at a higher incidence in the Total NB group compared with the placebo group were shifts to low leukocyte and low lymphocyte values. There were no notable differences between the Total NB and placebo groups in the incidences of potentially clinically significant hematology values, and there were no apparent dose-responsive effects.

No meaningful changes in chemistry parameters were observed in the NB clinical program, with the exception of those parameters discussed previously, including mean decreases in hs-CRP (Section 6.9.1.3) and improvements in the lipid and glycemic profile (Section 6.9.1.2 and 6.9.2, respectively). No meaningful increases in creatinine after long-term treatment with NB were observed; mean values at baseline, endpoint, and maximum were all within normal ranges (as discussed in Section 7.6.6). The increases in mean creatinine are likely due to inhibition of OCT2 and not indicative of changes in creatinine clearance as indicated by the lack of treatment effects on BUN. No potential hepatotoxicity was observed with long-term NB treatment and there were no apparent dose-responsive effects (Section 7.6.6).

7.7.1.2 Comparison of Diabetic and Nondiabetic Datasets

There were no apparent differences in the hematology and chemistry profiles in patients with diabetes compared to patients without diabetes with the exception of shifts to high creatinine, which occurred at a higher incidence in patients with diabetes than patients without diabetes (Section 7.6.6.1).

7.8 Electrocardiograms

As part of the agreed upon development program a comprehensive ECG analysis was conducted across the Phase 3 program. The analysis included ECG measurements in approximately 2775 patients receiving NB and 1393 patients on placebo at multiple time points over the course of treatment. Descriptive statistics of QT, QTcF and QTcB were evaluated by dose, and QTcF and QTcB were grouped for analysis at 2-hour intervals following dosing, including over 800 ECGs examined at 2 to 4 hours, the time corresponding to C_{max}. In general, there were no important differences between NB and placebo treatment in ECG intervals, including corrected QT (Table 48). Analysis by time interval since last dose indicate no adverse effects on cardiac repolarization, including timepoints when plasma concentrations of naltrexone, bupropion, or their metabolites were likely at or near maximum (i.e., at C_{max}).

In the NB clinical trials, there was no evidence of treatment-related QTc prolongation in NB-treated patients compared with placebo. Neither naltrexone nor bupropion alone are reported to prolong the QTc interval or cause rapidly activating delayed rectifier K+ current (iKr) blockade.

Table 48 Treatment-Emergent Electrocardiogram Results in Patients with Normal Baseline Measurements: Primary Dataset, Double-Blind Treatment Phase

	Placebo		NB16		NB32		Total NB	
ECG Parameter	N	n (%)	N	n (%)	N	n (%)	N	n (%)
QTcF								
>450 msec[a]	1364	48 (3.5%)	515	14 (2.7%)	2155	57 (2.6%)	2701	72 (2.7%)
>480 msec[b]	1393	2 (0.1%)	527	1 (0.2%)	2212	3 (0.1%)	2770	4 (0.1%)
>500 msec (PCS High)[c]	1393	0	527	0	2213	0	2772	0
≥30 msec from BL[a]	1364	82 (6.0%)	515	30 (5.8%)	2155	116 (5.4%)	2701	147 (5.4%)
≥60 msec from BL[a]	1364	5 (0.4%)	515	4 (0.8%)	2155	11 (0.5%)	2701	15 (0.6%)

a. Patients with a value >450 msec at baseline were excluded.
b. Patients with a value >480 msec at baseline were excluded.
c. Patients with a value >500 msec at baseline were excluded.
Abbreviations: PCS=potentially clinically significant; Total NB=all doses of combination naltrexone and bupropion treatment including NB48.

Diabetic patients showed a higher incidence of increased QTcF values ≥30 msec and ≥60 msec above baseline and >450 msec total for both the NB32 and placebo groups compared to patients without diabetes (Table 49). However, none of these changes required alterations in treatment or intervention, and none were considered precursors to significant clinical events.

Table 49 Treatment-Emergent Electrocardiogram Results: Diabetic and Nondiabetic Datasets, Double-Blind Treatment Phase

	Nondiabetic Dataset				Diabetic Dataset	
	Placebo (N=1346)		NB32 (N=2212)		Placebo (N=169)	NB32 (N=333)
ECG Parameter	N	n (%)	N	n (%)	n (%)	n (%)
QTcF						
>450 msec[a]	1207	41 (3.4%)	1874	48 (2.6%)	7 (4.1%)	10 (3.0%)
>480 msec[b]	1232	0	1922	1 (<0.1%)	NA	NA
>500 msec (PCS)[c]	1232	0	1923	0	0	0
≥30 msec from BL	1232	70 (5.7%)	1923	86 (4.5%)	13 (7.7%)	31 (9.3%)
≥60 msec from BL	1232	3 (0.2%)	1923	7 (0.4%)	2 (1.2%)	5 (1.5%)

a. Patients with a value >450 msec at baseline were excluded.
b. Patients with a value >480 msec at baseline were excluded.
c. Patients with a value >500 msec (nondiabetic patients) or ≥500 msec (patients with diabetes) were excluded.
Note: Data for ≥30 msec and ≥60 msec from baseline were included for the Nondiabetic Dataset to match the data analyzed for the Diabetic Dataset (both include patients with a baseline QTcF value >450 msec).
Abbreviations: NA=not available; PCS=potentially clinically significant.

7.9 Analysis of Safety in Subgroups

Analyses of AEs, AEs leading to treatment discontinuation, and vital signs (heart rate, SBP and DBP) were performed for subgroups of sex, age, ethnicity, race, ≥5% weight loss at endpoint, baseline smoking status, antihypertensive use at baseline, obesity class, CV medical history (vitals only), and dyslipidemia status at baseline (vitals only). The results are discussed in the individual sections for AEs (Section 7.4.2.1), AEs leading to treatment discontinuation (Section 7.4.4), and vital signs (Section 7.6.1.1.6). Summary data are presented in Appendix 8, Table 74 (AEs), Table 75 (SBP), Table 76 (DBP), and Table 77 (heart rate).

Based on the results of subgroup analyses, the following conclusions can be drawn:

- Although the number of elderly patients studied with NB is low (n=62, Primary Dataset), elderly patients may have an increased risk for central nervous system AEs (e.g., dizziness, tremor) or hypertension.

- Based on data from the NB clinical development program and consistent with labeling for naltrexone and bupropion, there are no unique dosing recommendations based on sex, age, race, or ethnicity.

- Based on data from the NB development program, there are no unique dosing recommendations for patients who smoke, use antihypertensive medications, or with complicated obesity, dyslipidemia, or a history of CV events.

7.10 Use in Pregnancy and Lactation

The use of any weight loss agent during pregnancy or lactation is not recommended.

7.10.1 Use in Pregnancy

Nonclinical and clinical results are described below from studies using naltrexone or bupropion as a single agent. Both naltrexone and bupropion are currently Pregnancy Category C medications for their approved indications. A brief summary of the outcome of pregnancies occurring during the NB Development program are also included in this section. There are no studies of NB in pregnant women or animals.

7.10.1.1 Results from Nonclinical studies

Separate developmental and reproductive toxicity studies with bupropion and naltrexone have been conducted in rats and rabbits.

Naltrexone administered orally has been shown to increase the incidence of early fetal loss in rats administered ≥30 mg/kg/day (180 mg/m^2/day) and rabbits administered ≥60 mg/kg/day (720 mg/m^2/day), doses at least 9 and 36 times, respectively, the maximum recommended human dose [MRHD] of naltrexone on a mg/m^2 basis.

Bupropion was administered orally in studies conducted in rats and rabbits at doses up to 450 and 150 mg/kg/day, respectively (approximately 12 and 8 times the MRHD, respectively, of the bupropion component in Contrave 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 primarily related to skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately 1.3 times 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 300 mg/kg/day (approximately 8 times the MRHD of the bupropion component in Contrave on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

7.10.1.2 Naltrexone or Bupropion Clinical Experience

There is limited data for naltrexone concerning potential for birth defects. In a review of naltrexone studies by Farid et al (2008), 46 of 1196 patients became pregnant while using oral naltrexone for opiate withdrawal. Of the known outcomes, there was no evidence of congenital malformations.

Pregnancy outcomes while using bupropion have been reported in a pregnancy registry sponsored by the bupropion manufacturer (GlaxoSmithKline), a retrospective cohort study, a retrospective case control study, and a prospective study.

- The purpose of the GSK International Bupropion Pregnancy Registry was to monitor for substantial increase in the frequency of major birth defects in pregnancies inadvertently or intentionally exposed to GSK brands of bupropion. Additionally, the Registry provided data on the types and frequency of pregnancy outcomes following exposure to bupropion. Healthcare professionals with patients exposed to bupropion during pregnancy were encouraged to prospectively enroll each patient in the registry. Reporting of exposed pregnancies was voluntary. To further reduce possible bias in reporting, the Registry asked healthcare providers to enroll their patients as early in pregnancy as possible, preferably before any prenatal testing for defects was done.

  At enrollment, information on maternal socio-demographics (age, ethnicity), pregnancy (date of last menstrual period, prenatal testing) and bupropion treatment (timing, dose, duration) was collected. Near the estimated date of delivery, follow-up was obtained through the healthcare provider including information on maternal risk factors, pregnancy outcome, and neonatal health. Data on exposure to bupropion and other medications during pregnancy were also reviewed. Exposure reports were considered ‘closed’ when unambiguous information on exposure and outcome had been obtained.

  The observed proportion of major birth defects in prospectively enrolled pregnancies with prenatal exposure in the first trimester and for whom outcome was available is 24/675 (3.6%, 95% CI 2.3% - 5.3%). This proportion includes 651 live births without birth defects, 18 live births with birth defects, 1 fetal death with a birth defect, and 5 induced abortions with birth defects. The overall proportion of major birth defects in metropolitan Atlanta reported by the Metropolitan Atlanta Congenital Defects Program (MACDP) from 1968 through 2003 was 2.67% (Correa et al., 2007).

After reviewing the prospectively reported pregnancy outcomes, the Bupropion Pregnancy Registry Advisory Committee concluded that the Registry had successfully met its primary purpose which was to exclude a major teratogenic effect in pregnancies inadvertently or intentionally exposed to any formulation of bupropion. The Registry was not designed to exclude increases in the risk of specific defects. The Committee noted an increase in the number of prospective reports of birth defects involving the heart and great vessels, as well as retrospective reports of cardiac defects, and that it was not possible to determine whether these data reflected a potential effect of bupropion on the developing cardiovascular system given the relatively small samples size and other limitations. To further evaluate a potential increase in cardiac malformations with bupropion and considering the limitations of the Registry (no adjustment for maternal demographics or underlying disease), the hypothesis generated by the registry data was tested in a managed-care database study.

- The retrospective managed-care database 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. (Wellbutrin SR prescribing information, 2010 [Appendix 1]).

- A report by Alwan et al. (2010) 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 pregnancies with reliably ascertained defects, including 64 cases of mothers exposed to bupropion between 1 month before and 3 months after conception, were compared with 5869 live born control infants with no major birth defects born in 1997-2004, including 26 cases of mothers who were exposed to bupropion during the same 4 month periconceptional window. There was no control for underlying maternal disease. Mothers of case infants were generally older, had a higher education level, were obese, smoked early in pregnancy, and had a lower family income compared with mothers of control infants. Other factors, such as having type 1 or 2 diabetes prior to pregnancy, a multiple pregnancy, or at least 1 previous live birth were more frequently reported among mothers of case infants than among mothers of control infants. Intended pregnancy, however, was reported more frequently among mothers of control infants. There was no association of major heart defects as a group and reported maternal bupropion use. Further analyses indicated a potential association between early pregnancy bupropion use and a specific and very rare left outflow tract heart defect, but not with other types of heart or non-cardiac defects.

- A report by Einarson et al. (2009) summarized the results of a large prospective cohort study of pregnancy outcomes of women exposed to antidepressants during pregnancy matched to a comparison group of pregnant women not exposed to teratogens or antidepressants. Antidepressant use during the first trimester of pregnancy among 928 women was not associated with an increased risk for major malformations. Specifically, there were no major malformations noted among the 113 women using bupropion.

7.10.1.3 Results from NB studies

Despite the requirement for all female patients of child bearing potential to use birth control, 21 (0.78%) women treated with NB and 7 (0.56%) women treated with placebo became pregnant. Of the 21 patients who became pregnant after NB exposure, all but one had at least 7 days of fetal exposure based on having a positive serum pregnancy test within 2 weeks of the last dose of study drug. One patient received only a single dose of NB16.

Treatment with NB was not associated with congenital defects. Patient-reported outcomes of the pregnancies in the NB clinical development program are presented in Table 50. Of the 21 NB patients who became pregnant, 11 patients carried to term and gave birth to healthy infants, three patients had elective terminations with no record of congenital defect, four patients experienced spontaneous miscarriages (one of whom had a history of ectopic pregnancy and another had a prior miscarriage), and the outcomes of three pregnancies were unknown (patients were lost to follow-up). There were no reports of congenital anomaly.

Table 50 Pregnancies in the Contrave Development Program, Primary Dataset, Women Only

	Placebo N=1247 n (%)	**Total NB N=2690 n (%)**
Pregnancies	**7 (0.56%)**	**21 (0.78%)**
Normal	5 (0.40%)	11 (0.41%)
Congenital abnormalities	0	0
Spontaneous miscarriage	1 (0.08%)	4 (0.15%)
Elective terminations	0	3 (0.11%)
Other/Unknown[a]	1 (0.08%)	3 (0.11%)

a. Includes one patient who reported that she was no longer pregnant approximately 2 months after her positive serum pregnancy test but did not provide additional details regarding pregnancy outcome.

N represents the number of female patients in each treatment group.

Abbreviations: Total NB=all doses of combination naltrexone and bupropion treatment.

7.10.1.4 Use in Lactation

Studies of NB in lactating women have not been conducted; however, naltrexone and bupropion and their metabolites have been shown to be secreted in breast milk (Wellbutrin SR prescribing information, 2010 [Appendix 1]; Chan et al. 2004).

7.11 Drug Abuse, Dependence and Overdose

Neither naltrexone nor bupropion is a controlled substance, and since their approval have not emerged as drugs with abuse or dependence potential. Bupropion post-marketing exposures worldwide exceed 50 million and has confirmed the lack of increased abuse liability as was reported in the original human laboratory studies evaluating abuse liability. Naltrexone also has a long legacy of human experience with over one million post-marketing exposures. Of note, both agents are indicated for use in populations at risk of drug abuse and dependence (naltrexone for alcohol and opiate dependence, bupropion for nicotine dependence). A review of NB safety information revealed that there were no deaths or SAEs attributable to

drug abuse or withdrawal, no overdoses, or evidence of drug diversion or inappropriate self administration.

No events characterized as overdose occurred in the NB program. Approved prescribing information and publications have described the sequelae of overdose with bupropion and naltrexone. Reactions to bupropion overdose when administered as a single agent include seizures, hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. The most common results of naltrexone overdose include gastrointestinal distress, somnolence, and dizziness.

7.12 Withdrawal and Rebound

Adverse events associated with withdrawal from NB were examined in Study NB-301, a 56-week safety and efficacy study that included an additional 2-week blinded discontinuation phase for those patients still enrolled at the end of the active treatment phase. The frequency and distribution of discontinuation AEs does not suggest any relationship to active treatment, dose, or method of drug discontinuation, nor is there any emergent pattern of events suggestive of a discontinuation syndrome. No indications of an effect of NB treatment on depressive or anxiety symptoms were observed on the IDS-SR for sudden or tapered discontinuation patients in the NB16 or NB32 groups.

7.13 Summary of Safety

The safety profile of NB has been well characterized in a large clinical program that included nearly 3500 NB treated patients overall and 2313 patient-years of exposure across a clinically relevant range of doses. The observed NB safety and tolerability profile was generally comparable to the well-established safety profiles associated with naltrexone and bupropion, each with more than 20 years of post-marketing experience and approximately 1 million and 50 million unique patient exposures, respectively (Wolters Kluwer and IMS Health). The individual doses of naltrexone and bupropion in the NB combination were within the approved doses for the individual components. Unlike the apparent synergy of the components for effect on weight loss, and with the possible exception of nausea and vomiting, the NB combination of naltrexone and bupropion did not appear to be associated with synergistic occurrence of adverse events.

The most common AEs in patients with obesity were nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea. The pattern of AEs in NB-treated obese/overweight patients with type 2 diabetes was generally similar to that of patients without diabetes. Overall, AEs mostly occurred early in treatment, were generally mild or moderate in severity, and were self-limited. The most common AEs leading to discontinuation in NB-treated patients (nausea, headache, dizziness, and vomiting) were generally consistent with the commonly reported AEs overall. Serious AEs were infrequent and, with the exception of cholecystitis/cholelithiasis events, equally distributed across treatment groups.

Safety information collected in the NB clinical development program was evaluated for adverse events historically associated with either bupropion or naltrexone therapy. Adverse events such as seizure occurred at an incidence of <0.1%, which is consistent with what has been previously described with bupropion monotherapy (0.1% with doses up to 300 mg).

NB therapy was not associated with an increase in depression, suicidal ideation, or suicidal behavior.

No clinically relevant changes in liver transaminases were observed in the NB clinical studies indicating a lack of hepatotoxicity attributable to naltrexone, as expected, since naltrexone doses selected for the NB combination (daily doses ≤48 mg) were below those associated with hepatotoxicity (daily doses >300 mg). Although there was a higher incidence of cholecystitis observed in association with NB therapy compared with placebo, this effect was likely a consequence of weight loss combined with the higher inherent risk for this population.

Major cardiovascular AEs based on various definitions (broad or custom) with and without revascularization procedures revealed generally balanced event rates between the placebo and NB treatment groups. While there was no evidence of increased CV risk associated with NB, the limited number of MACE events precludes definitive conclusions regarding the impact of NB on ischemic events. Across both treatment groups, the exposure adjusted incidence rate of MACE events was approximately 0.1 to 0.2/100 patient-years, which is generally consistent with predicted rates for a female middle-age obese population. The single death resulting from a presumed myocardial infarction occurred in an NB-treated patient with multiple pre-treatment cardiac risk factors.

Consistent with the known hemodynamic effects of bupropion, NB treatment was associated with increases of approximately 1 mm Hg in mean SBP and DBP early (at weeks 4 and 8) in treatment. By week 12, mean blood pressure returned to baseline with subsequent reductions below baseline. After 28 weeks of treatment, average changes in blood pressure from baseline for NB-treated patients were maintained at approximately 1 mm Hg below baseline values. Hypertension AEs were infrequent, and the proportion of patients with outlier values was low. In placebo-treated patients, both mean SBP and DBP decreased from baseline over the course of the study and resulted in Week 56 values averaging 1-2 mm Hg below baseline. For both placebo- and NB-treated patients, greater weight loss was associated with greater decreases in mean blood pressure, although BP reductions were less for NB-treated patients than placebo treated patients for any given weight loss. The incidences of SBP and DBP increases above pre-specified values (e.g., SBP ≥140 mm Hg; DBP ≥90 mm) were higher in the Total NB group than the placebo group, as were the incidences of relative increases from baseline (SBP ≥10 mm Hg; DBP ≥5 mm Hg). Outlier values, however, were not usually sustained, and hypertension AEs were infrequent in both treatment groups.

NB treatment was associated with generally small (1-3 bpm) increases in heart rate above baseline. The occurrence of outlier values was low and predominantly transient, occurring with a slightly greater frequency in NB-treated patients compared with placebo-treated patients. Arrhythmia-type AEs occurred at a somewhat higher incidence in NB-treated patients (5.5%) than in placebo-treated patients (4.2%). This increase was largely due to palpitations, with smaller increases noted for tachycardia and increased heart rate events. Importantly, no increase in syncope was observed and ECG findings were similar between the treatment groups. There was no treatment effect on QTc intervals and no relationship between interval duration and drug concentration was evident.

Clinically meaningful changes in chemistry parameters observed in the NB clinical program included mean decreases in hs-CRP and improvements in the lipid and glycemic profile

(discussed in efficacy). Mild increases in creatinine after long-term treatment with NB were observed; mean values at baseline, endpoint, and maximum were within normal ranges. This is likely due to inhibition of OCT2 and not indicative of changes in creatinine clearance as indicated by the lack of treatment effects on BUN. There were no other clinically meaningful changes in laboratory findings, physical examinations, or ECGs. Pre-specified safety topics of special interest occurred with a frequency and severity expected for the treatment population or else consistent with the known safety profile of the approved NB constituents. The NB safety profile is considered readily manageable via appropriate patient selection, informed prescribing, appropriate patient care, and prompt discontinuation of NB for patients who do not lose at least 5% of their body weight within 4 months of initiation of their treatment, or experience persistent significant elevations in blood pressure or heart rate in the same time frame.

8 BUPROPION POSTMARKETING EXPERIENCE AND RELEVANCE TO NB SAFETY EVALUATION

8.1 Relevance of Bupropion Patient Population

Bupropion is a well characterized agent that has been used by over 50 million individual patients since initial approval. In 2009, approximately 6 million patients were prescribed bupropion for a range of depressive disorders and as an aid to smoking cessation. Because important aspects of the safety profile of the NB combination, including cardiovascular effects and seizures, are the result of the bupropion component, it is appropriate to consider the bupropion patient experience for overall evaluation of NB. As demonstrated below, the population of patients receiving bupropion therapy has important similarities to patients enrolled in the NB clinical program as well as the population of patients who receive currently marketed obesity pharmacotherapy. In addition, clinical experience and investigation in relevant patient populations, including those with cardiovascular risk factors or established cardiovascular disease, have not identified specific safety signals for clinical cardiovascular events.

Using a validated patient survey methodology (Wolters Kluwer), demographic and clinical characteristics were summarized for patients receiving bupropion and patients receiving obesity pharmacotherapy (e.g., orlistat, phentermine, sibutramine). Table 51 highlights that bupropion users, the population of patients who currently seek out obesity pharmacotherapy, and patients enrolled in the NB clinical program have several important similarities:

- Populations are predominantly middle-aged, white females
- Prevalence of established cardiovascular disease is low (<5%)
- Prevalence of cardiovascular risk factors (e.g., diabetes, hypertension, dyslipidemia) is generally similar

Most importantly, the distribution of BMI among patients receiving bupropion reveals a considerable overlap between the currently indicated uses of bupropion and the presence of overweight/obesity. The average BMI of bupropion users is 30.9, and approximately 68% have a BMI of $\geq$27 kg/m^2. Accordingly, in 2009 there were approximately 4 million overweight or obese patients who received bupropion therapy. These data corroborate the known association between obesity and depressive disorders (Petry et al., 2008), and highlight that bupropion is a commonly prescribed antidepressant among obese patients.

Table 51 also suggests that:

- The NB clinical program enrolled a representative sample consistent with patients who currently receive obesity pharmacotherapy, the population intended for commercial use of Contrave.
- The similarities between patients receiving bupropion and those enrolled in the NB clinical program increases the relevance of examining the large clinical safety experience with bupropion over 20 years of approved use.

Table 51 Demographic and Baseline Characteristics for Bupropion, Contrave, and Other Obesity Pharmacotherapies

	Bupropion[a] N=1,472,754	Contrave Phase 3 Program[b] N=4536	Obesity Pharmacotherapy[a,c] N=393,989
Mean Age (years)	47.2	45.6	43.0
Female (%)	66.4	82.6	83.6
White (%)	90.5	77.4	84.8
Mean BMI (kg/m^2)	30.9	36.3	32.2
CV disease (%)	3.6	1.3[d]	1.6
T2DM (%)	12.8	11.1	12.2
Dyslipidemia (%)	33.5	54.2	31.2
Hypertension (%)	33.1	24.6	30.4

a. Validated patient survey methodology performed by Wolters Kluwer.
b. Includes all randomized patients.
c. Includes orlistat, phentermine, and sibutramine.
d. Patients with a history of ischemic heart disease in Primary Dataset.
e. Patients with a history of depression.

8.2 Clinical Cardiovascular Experience with Bupropion

Bupropion has not been investigated in long-term cardiovascular outcome trials. Information on the clinical safety experience with bupropion comes from review of regulatory approvals and labeling, clinical and scientific literature, and examination of spontaneous adverse event reporting through FDA's Adverse Events Reporting System (AERS). Specifically with regard to bupropion's cardiovascular safety:

- Effects on blood pressure and heart rate are well characterized and appropriately referenced in labeling.
- Bupropion has been studied in populations at higher risk for cardiovascular events, including:
    - Major depression
    - Smoking cessation
    - Established cardiovascular disease
    - Hypertension

Large prospective patient registries and examination of AERS have not identified evidence of increased clinical cardiovascular events. Reviews of bupropion therapy have noted that it is considered an appropriate therapy in patients with established cardiovascular disease (Taylor et al., 2008; Thorndike and Rigotti, 2009).

8.2.1 Review of Regulatory Approvals and Labeling

Approved labeling for bupropion across a range of depressive disorders and as an aid to smoking cessation highlights that adverse events of hypertension can occur in clinical practice. While the reported occurrence of hypertension events is low, the Precautions section of bupropion labeling makes specific reference to the risk for hypertension,

particularly when bupropion is combined with nicotine replacement. Importantly, labeling notes that the safety of bupropion in patients with a recent history of myocardial infarction or unstable heart disease has not been definitively established and that care should be exercised when bupropion is used in these patients.

8.2.2 Studies in Patients at Risk for Cardiovascular Disease

Bupropion has been studied in several patient populations relevant to cardiovascular disease. Major depression itself is associated with a cardiovascular risk, with epidemiological studies suggesting a 50% to 100% increase in the risk of cardiovascular events among patients with depression compared to patients who are not depressed (Lett, 2004; Van der Kooy et al., 2007). Nicotine dependence is a clear cardiovascular risk factor and smoking cessation is also a major indication for the use of bupropion. As referenced above, no specific cardiovascular event signals have been raised in these populations, however, appropriate caution is noted in labeling with regard to hypertension and active cardiovascular disease.

Additionally, bupropion has been investigated in placebo controlled trials among patients with established cardiovascular disease, including a trial of 629 smokers with cardiovascular disease (Tonstad et al., 2003) and a trial of 248 smokers hospitalized for acute myocardial infarction and randomized in hospital to bupropion or placebo therapy as an aid to smoking cessation (Rigotti et al., 2006). While bupropion use in these studies was short (7-12 weeks), the exposure corresponds to the period of greatest pressor effect with NB. During exposure and over one year of follow up, blood pressure did not differ between treatment groups and no cardiovascular event signals were identified.

Thase et al. (2008) investigated the short term (4 week) impact of blood pressure and heart rate of bupropion compared to placebo in 300 patients with mild, untreated hypertension. Similar findings to the NB clinical program were observed, including approximately 1-2 mm Hg increase in blood pressure compared to placebo and an increase in heart rate of approximately 1-2 bpm. Importantly, a 24-hour ambulatory blood pressure monitoring (ABPM) examination at Week 4 demonstrated similar results to the NB-303 24-hour ABPM substudy. This study did not follow cardiovascular events, but did demonstrate among hypertensive patients that the effects of bupropion remain small and consistent with changes observed in other patient populations.

Bupropion monotherapy has also been investigated in obese patients (Anderson et al., 2002), including those with depressive symptoms (Jain et al., 2002). Jain et al. randomized 422 patients to receive bupropion 300 to 400 mg/day or placebo for 26 weeks. The bupropion group lost an average of 4.6% from baseline bodyweight compared to 1.8% in placebo patients. Blood pressure was unchanged in the bupropion group compared to a reduction of approximately 2 mm Hg with placebo. Heart rate increased by 1 bpm from baseline compared to placebo. Serious AEs were slightly more frequent in the placebo group and no concern with regard to cardiovascular events was identified.

Thus, bupropion has been investigated across a spectrum of patient populations at high risk for cardiovascular events as well as in lower risk obese patients with depressive symptoms. While no large, randomized clinical outcomes trials have been conducted, the results of these smaller trials are generally regarded as supportive of the safety of bupropion in these patient populations.

8.2.3 Large Patient Cohorts and Spontaneous Reporting of Adverse Events with Bupropion

Several longitudinal cohort and database studies have examined the safety of bupropion in real world settings. Boshier et al. (2003) conducted a prospective observational cohort examination of approximately 11,700 patients receiving bupropion for smoking cessation. Adverse events and mortality were ascertained over 12 weeks after initiating therapy. Common adverse events reported during the observation period are consistent with bupropion labeling. Standardized mortality ratio was 0.77 (95% CI 0.42, 1.28), which the authors interpret as providing no evidence of a higher mortality rate among bupropion users. Hubbard et al. (2005) used a computerized general practice database to examine bupropion use in smoking cessation. Data from approximately 9,300 patients were extracted for the occurrence of seizure and mortality using the self-controlled case series method. Results suggest that bupropion use is likely associated with an increased risk of seizure (relative incidence 3.62; 95% CI 0.87, 15.09), but no evidence was found to suggest an increase in mortality (relative incidence 0.50; 95% CI 0.12, 2.05). A bupropion post-approval surveillance study was performed across 50 centers in South Korea between 2002 and 2008. Approximately 2,400 patients were followed for adverse events, and the results demonstrate a profile consistent with labeling. Most common events were nausea, insomnia, dizziness, dry mouth and headache. No information on the occurrence of seizure or cardiovascular events was provided and no SAEs considered related to bupropion were reported.

In addition to the above literature, an analysis using adverse event reports submitted to the FDA's AERS was performed to assess whether bupropion (N=30,122 reports) has similar reporting rates for major adverse cardiac events (MACE) and seizure events when compared to relevant controls including commonly prescribed antidepressants (i.e., fluoxetine, N=55,240 reports; venlafaxine, N=21,232 reports) and smoking-cessation drugs (i.e., varenicline, N=14,373 reports). MACE was defined by preferred terms (PTs) for stroke and transient ischemic attack, acute myocardial infarctions, and cardiovascular mortality, and seizure by PTs for convulsion and partial convulsion, seizure and partial seizure, epilepsy, and postictal paralysis. [4] Formal signal detection analysis was performed using the proportional reporting ratio (PRR) and the Multi-item Gamma Poisson Shrinker (MGPS) methods, per the FDA's Guidance for Industry on Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Acknowledging the limitations associated with signal detection using spontaneous reporting in the AERS system, key findings are summarized below:

- Bupropion has no signal for MACE when compared to fluoxetine and venlafaxine: the finding is consistent across all bupropion brands and formulations combined.
- Bupropion when used as Zyban for smoking cessation has no signal for MACE when compared to varenicline.
- Bupropion in Wellbutrin formulations have some reporting signals for seizure.

[4] The complete list of preferred terms considered in each category of AEs and stratification will be provided upon request.

In conclusion, the clinical cardiovascular experience with bupropion since approval appears relevant because NB's pressor effect is derived from the bupropion component and because the patient population using bupropion has important similarities to the patient population intended for NB use. Examination of the available bupropion experience through regulatory review and labeling, published literature, and investigation of spontaneous adverse event reports confirms the finding of pressor effect, but does not identify any specific finding for major cardiovascular events. While no large, randomized clinical outcomes trials have been conducted, the cumulative experience with bupropion is generally regarded as supportive of the safety of bupropion in a variety of patient populations, including those at higher risk for cardiovascular events.

9 RISK MITIGATION

9.1 Overview

The introduction of a new obesity pharmacotherapy requires careful consideration of risk management. The proposed plan was created to minimize or mitigate known risks and research unknown potential risks. Key elements of the plan include 1) labeling and Risk Evaluation and Mitigation Strategies (REMS), 2) a launch program that focuses on appropriate use of Contrave and evaluates program effectiveness, and 3) a research program to monitor the utilization of Contrave and investigate the impact on clinical outcomes.

The goals of the Contrave risk mitigation plan are as follows:

1. To inform HCPs and patients about the potential serious risks associated with the use of Contrave.
2. To inform HCPs and patients about patient selection criteria and safe use of Contrave.
3. To continuously assess the safety profile of Contrave utilizing active and passive surveillance in addition to a targeted clinical cardiovascular outcome study.
4. To incorporate newly acquired safety information into risk mitigation tools.

To address these goals, targeted materials will be used to educate HCPs and patients on the Contrave risk-benefit profile, appropriate prescribing, and safe use. Table 52 provides an overview of the tools that will be available. Program assessments will be employed to gauge whether the risk mitigation plan goals are being met.

All REMS materials will be tested prior to their first use and then serially evaluated by a combination of knowledge, attitude and behavior surveys, chart reviews and/or a representative survey of anonymized patient electronic records to assess:

- Physician and patient comprehension of REMS materials
- Adherence to REMS recommendations
- Outcomes associated with Contrave therapy, including weight change (as available) and targeted AEs

Table 52 Education and Communication Tools

Educational Components	HCPs	Patients
REMS		
• Full Prescribing Information*	X	
• Medication Guide*	X	X
• Prescriber Introductory Letter*	X	
• Pharmacy Introductory Letter	X	
• Pharmaceutical Compendia Introductory Letter	X	
• Healthcare Professional Education Program Kit		
• Prescribing Brochure	X	
• Patient Management Algorithm	X	
• Patient Screening Form	X	
• Prescriber-Patient Counseling Guide	X	X
• REMS Web Site	X	X
Appropriate Use Program and Support Tools		
• HCP Education and Training		
• Clinical Patient Assessment and Monitoring Tools	X	
• Certified Education Center	X	
• Continuous Patient Education and Support		
• Initiation Education Kit		X
• Self-Assessment and Monitoring Tools		X
• Continuous Online Obesity and Treatment Education		X
• Lifestyle Modification Support Program		X
• Product Web Site	X	X

*Also included in the Healthcare Professional Education Program Kit

9.2 Labeling and REMS Components

9.2.1 Full Prescribing Information (PI)

The Contrave PI language will specifically highlight known risks related to the use of the approved individual constituents. This includes the Boxed Warning regarding the risk of suicidality with antidepressant drugs when used in younger patients, as well as the risk of seizure. In addition, specific instruction regarding recommended actions in the face of insufficient weight loss or persistent clinically relevant increases in blood pressure or heart rate will also be provided, as shown below in excerpted text from the proposed prescribing information.

> **USPI Section 2.1, Recommended Dosing.** Most patients who respond to Contrave will have done so by 4 months of treatment. If a patient has not exhibited clinically meaningful weight loss (e.g., at least 5%) after 4 months

of treatment, the physician should consider discontinuation of Contrave and initiation of other weight management strategies should be considered.

Patients may experience elevated blood pressure or pulse during Contrave treatment; the risk may be greater during the initial 3 months of therapy. If clinically relevant and sustained (e.g., at least two consecutive measurements) increases in blood pressure or pulse occur, Contrave should be discontinued. As patients with hypertension or a history of hypertension may be at increased risk of blood pressure elevations, care should be exercised when initiating treatment with Contrave in such patients.

USPI Section 5.5, Warnings and Precautions – Hypertension. Blood pressure and pulse should be measured prior to starting therapy with Contrave and should be monitored at regular intervals thereafter for the first 4 months of treatment. If patients experience a clinically relevant and sustained (e.g., at least two consecutive measurements) increase in blood pressure or pulse while receiving Contrave, treatment should be discontinued. Contrave should be given with caution to those patients with hypertension or a history of hypertension (see Dosage and Administration), and should not be given to patients with inadequately controlled hypertension (see Warnings and Precautions).

There is no clinical experience establishing the safety of Contrave in patients with a recent history of myocardial infarction or unstable heart disease. Contrave should be used with caution in patients with active coronary artery disease (e.g., ongoing angina or recent history of myocardial infarction) or cerebrovascular disease (stroke or transient ischemic attack (TIA)).

The PI also includes considerable information to guide appropriate patient selection, including the specific contraindications.

USPI Section 4, Contraindications. Contrave is contraindicated in patients:

- with inadequately controlled hypertension
- with a seizure disorder or a history of seizures
- treated with any other medication containing bupropion
- who have bulimia or anorexia nervosa
- currently dependent on chronic opioids or opiate agonists (e.g., methadone), or patients in acute opiate withdrawal
- receiving concomitant administration of monoamine oxidase inhibitors (MAO Inhibitors). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with Contrave
- who have shown an allergic response to bupropion, naltrexone or any other component of Contrave

The Contrave PI is provided with each bottle and is also included with educational material for HCPs. In addition, HCPs may access the PI through the REMS and product web sites.

9.2.2 Medication Guide

Primary communication to patients will be via the Contrave Medication Guide. The Medication Guide contains information on both the risks and safe use of Contrave. The information included in the Medication Guide is presented in easy-to-understand language that is appropriate for patients (seventh grade health-literacy).

Qualitative comprehension testing of the Medication Guide has been conducted in subjects, including those with low health-literacy. The testing was conducted as one-on-one, in-depth interviews to review written material with participants after they read the Medication Guide. The study results showed that the individuals tested understood the information as presented in the Medication Guide.

A Medication Guide will be dispensed with each Contrave prescription. To ensure compliance with Title 21 of the Code of Federal Regulations (21 CFR) §208.24, sufficient numbers of the Medication Guide will be provided to distributors and authorized dispensers.

- One copy of the Full PI, which includes the Medication Guide, will be included with each bottle of Contrave.
- The bottle label will include a statement instructing the authorized dispenser to provide a copy of the Medication Guide with each Contrave prescription.
- The Medication Guide will be distributed with the Contrave REMS Healthcare Professional Education Program Kit.
- The Medication Guide will be available through the product web site REMS web site.

9.2.3 Healthcare Professional Education Program Kit

The REMS program will ensure that education is provided to HCPs who prescribe Contrave. Education will be conducted under a detailed REMS Communication Plan. The purpose of the plan is to appropriately communicate:

- The potential serious risks associated with the use of Contrave, including suicidal thinking and behavior, seizures, and cardiovascular effects
- Patient selection considerations
- Dosing and administration
- The importance of a therapeutic trial to evaluate efficacy response and monitor blood pressure and heart rate effects
- Periodic evaluation of chronic use
- The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read the Medication Guide

The HCP Education Program Kit contains the following materials:

- Dear Healthcare Professional Letter detailing potential serious risks
- Full Prescribing Information (described earlier)
- Medication Guide (described earlier)
- Prescribing Brochure
- Patient Management Algorithm
- Patient Screening Form
- Prescriber-Patient Counseling Guide

Within 60 days of approval of Contrave, the HCP Education Program Kit will be direct-mailed to prescribers identified as those most experienced in treating obesity, including primary care physicians and endocrinologists. Additional printed materials will be made available through field-force distribution, the medical services department, and the REMS web-site. Prescribers will be re-educated every 2 years or following substantial changes to the REMS, including revisions to the PI or Medication Guide. The unique components of the kit not discussed earlier are described in the following sections.

9.2.3.1 Prescribing Brochure

The Prescribing Brochure (see Appendix 9, Figure 44) contains the essential information for HCPs who prescribe Contrave and describes other core risk mitigation tools such as the Patient Management Algorithm, Patient Screening Form, and the Prescriber-Patient Counseling Guide

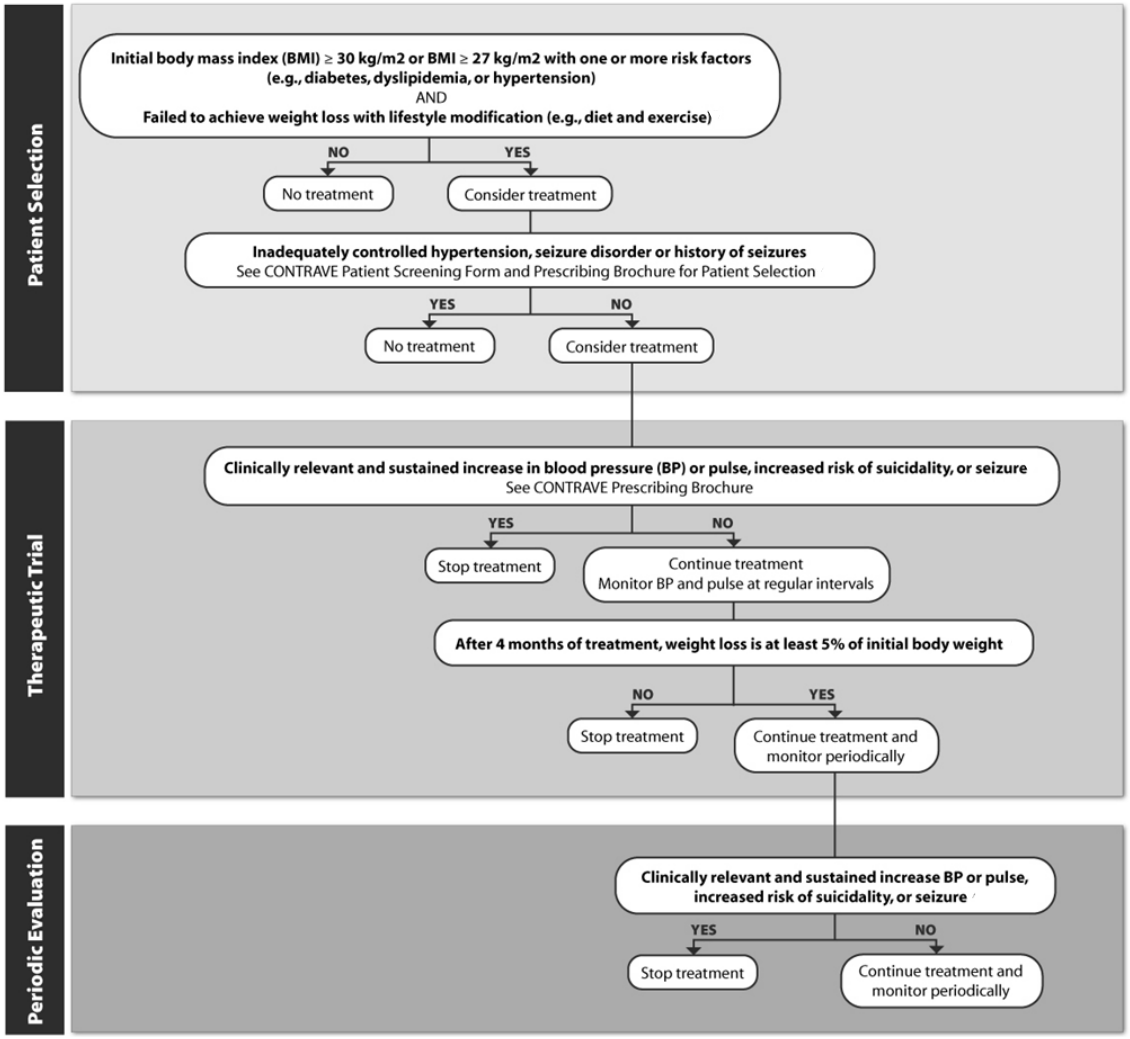
9.2.3.2 Patient Management Algorithm

The Patient Management Algorithm (see Figure 36) which is intended to help inform patient selection and management decisions, has been developed based on analyses of data from the Contrave clinical development program. Based on these analyses, two key variables emerged as the most relevant to inform appropriate patient management, specifically (1) early weight loss as a predictor of one year weight loss and (2) early blood pressure changes as a predictor of long-term blood pressure elevations. As seen in Figure 36 and presented in more detail below, it is these two variables that comprise the main elements of the algorithm and support the use of a therapeutic trial.

> **Weight Reduction.** Analyses were conducted to evaluate whether earlier weight loss (Weeks 4-28) is predictive of a 5% or greater weight loss response at week 56. Based on receiver operating characteristic curves 5% weight loss from baseline at Week 16 showed 75 to 85% accuracy in the four Phase 3 trials in identifying 5% responders at Week 56 with fair balance between sensitivity and specificity. Additionally, in a pooled analysis of the four Phase 3 trials, among the NB32 subjects who achieved ≥5% weight loss at Week 56 based on LOCF, more than 85% reached the responder status by Week 16.
>
> **Blood Pressure and Heart Rate.** Odds ratios based on logistic modeling were used to assess whether the occurrence of late outliers (Weeks 28-56) of blood pressure and heart rate could be predicted based on the occurrence of early outliers (Weeks 4-16). For this assessment outliers were defined as at least 2 consecutive increases in the vital sign parameter ≥10 units relative to baseline during the early and/or late time period. Patients with an earlier SBP outlier had at least 12 times the odds of having outlier values late in treatment, compared to those without early outliers. Similar findings were noted for DBP and heart rate.

Based on these analyses it is anticipated that close monitoring and management of these parameters may be useful in selecting appropriate patients for continued Contrave treatment and in stopping therapy for patients developing meaningful blood pressure or HR increases, or achieving insufficient weight loss (<5%).

Figure 36 Patient Management Algorithm



Implementation of the Algorithm will be supported by the following tools, which are also included in the HCP Education Program Kit.

9.2.3.3 Patient Screening Form

The Patient Screening Form will be used to guide HCPs in the proper selection of patients for Contrave treatment in order to mitigate the primary risks associated with the use of Contrave (see Appendix 9, Figure 45).

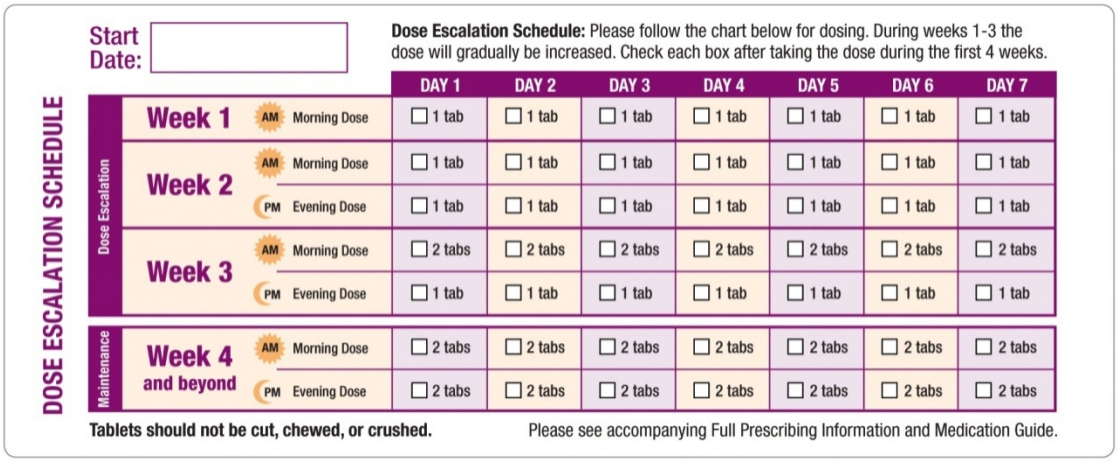
9.2.3.4 Prescriber-Patient Counseling Guide

The Prescriber-Patient Counseling Guide will be used to aid HCPs in the proper counseling of patients who are candidates for Contrave therapy. This Guide will include information on Contrave risks and safe use in an easy to read format (e.g., Frequently Asked Questions) and is intended to be distributed to patients. In addition, the guide will include information on the importance of reading the Medication Guide dispensed with each prescription as well as providing the Dose Escalation Schedule (Figure 37) as a perforated card.

9.2.3.4.1 Dose Escalation Schedule

The Dose Escalation Schedule is used to educate patients on the correct dosing initiation and dose escalation of Contrave treatment (see Figure 37). In addition to being provided attached to the Prescriber-Patient Counseling guide, this information is included on the bottle label.

Figure 37 Dose Escalation Schedule



9.2.4 REMS Web Site

The Contrave REMS web site (www.contraverems.com) will contain information about the REMS program and serves as one method by which prescribers can become educated on the risks and safe use of Contrave (see Appendix 9, Figure 46). The web site also contains the appropriate forms and resources to facilitate proper prescribing and safe use. The web site is referenced in the REMS-related materials provided to prescribers and patients. It also serves as a resource for accessing all REMS educational materials.

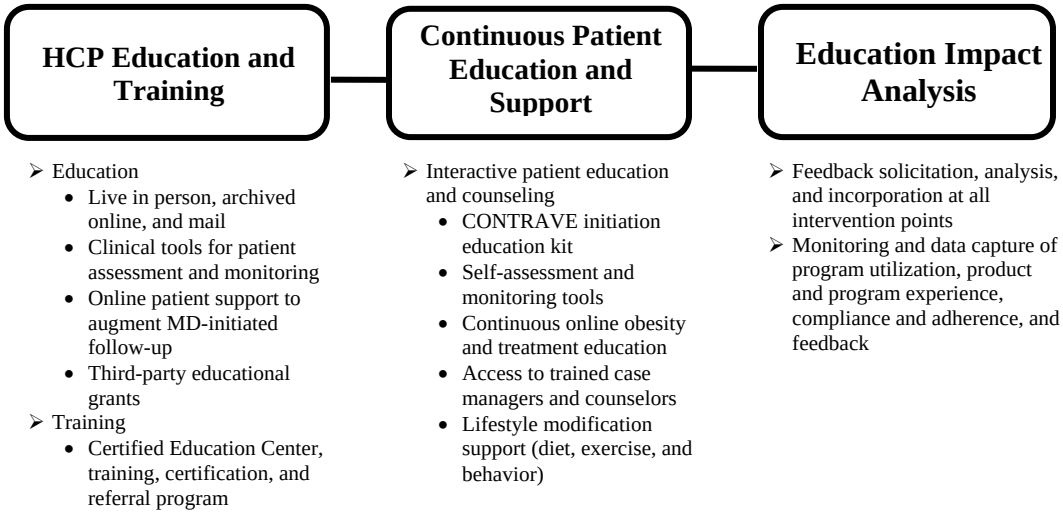
9.3 Appropriate Use Program and Support Tools

The Appropriate Use Program (AUP) is designed to complement the REMS program by supporting accurate patient selection by clinicians, evaluation of medication effectiveness, assisting with treatment discontinuation among non-responders, and providing monitoring and support tools throughout the duration of care. To achieve these goals, education for appropriate and informed use will be integrated throughout all manufacturer-supported communications and will be accompanied by clinical tools designed for practical use at the individual HCP and patient levels. Program objectives include the following:

- **Disease state education:** Increase HCP, caregiver, and patient knowledge of cardiometabolic health and standards of care in weight loss intervention.
- **Contrave appropriate use education:** Provide HCPs, caregivers, and patients with information on safety and prescribing, and provide tools for identifying appropriate patients and assessing treatment effectiveness and appropriate treatment duration.
- **Continuous support program:** Equip physicians, caregivers, and patients with a comprehensive behavior modification program that emphasizes and supports the health benefits of sustained weight loss.

The program includes three major components: HCP education and training, continuous patient education and support, and education impact analysis. The program will be modeled after successful weight loss management initiatives such as The Weight Loss Maintenance Group, The Diabetes Prevention Program, the Look Ahead Trial, and the Mayo Clinic EmbodyHealth Solutions. Figure 38 depicts in schematic form the three major sections of the educational program design, which are also described in more detail below.

Figure 38 AUP Educational Program



HCP Education. An element of the Contrave education program is an interactive, HCP education and training program designed in collaboration with a steering committee comprised of experts and specialty-specific working groups to educate and train HCPs on important topics, including the following:

- Disease-state mechanisms, diagnosis, and comorbidities
- Multidisciplinary treatment and monitoring strategies and standards of care
- Contrave appropriate use, risks, and prescribing information
- Use of the online patient support program for Contrave appropriate use, adherence and outcomes improvement, and support for treatment discontinuation when necessary

Certified Education Center. A manufacturer-supported, third-party Certification Program, coordinated with The Obesity Society's Certified Obesity Medical Physician (COMP) initiative, will be evaluated as a possible means of supporting clinician effectiveness in weight loss intervention and connect motivated patients to educated prescribers.

Continuous Patient Support. This physician-directed online patient program is designed to provide continuous educational support that improves long-term adherence to the weight loss intervention plan in conjunction with Contrave appropriate use. Program goals are to:

- Provide patients, physicians, and online counselors with timely and key biometric and health assessment data to track, monitor, and report health and wellness performance and manage risk
- Educate on initiation and ongoing management with the prescribed regimen
- Support adherence and long-term commitment to food and exercise behavior modification

The HIPPA-compliant program web site is designed to serve as a communication and support hub for patients, HCPs, and online counselors. Program elements being evaluated would provide patients with user-friendly tools, education, and support through a team-based approach to successful weight loss and maintenance. Patients would access the program through a HCP.

9.3.1 Product Web Site

The Contrave web site (www.contrave.com) will contain product information as well as information and resources about appropriate use. This web site also contains supplemental resources and support tools, as described in Section 9.3, to facilitate appropriate prescribing and safe use, and will provide a link to the REMS website described earlier.

9.4 Assessments

The following sections summarize the sources of information that will be used in conducting periodic assessments of the extent to which the REMS and AUP goals are being met, or whether the goals or particular elements of each program should be modified.

9.4.1 Patient and Prescriber Knowledge, Attitude, and Behavior Surveys

Knowledge, Attitude, and Behavior (KAB) surveys will be conducted with patients in order to assess their comprehension of the serious risks of Contrave as outlined in the REMS objectives. The patient surveys will also measure pharmacy compliance with distribution of the Medication Guide.

KAB surveys will be conducted with prescribers in order to assess their comprehension of the serious risks of Contrave therapy as outlined in the REMS objectives. The prescriber surveys will also measure understanding of appropriate prescribing and safe use of Contrave.

The survey period, for both patients and prescribers, will begin approximately six months after approval of the REMS and will be repeated prior to each assessment timepoint.

The methodology and protocol for the KAB surveys and the survey instrument will be developed after the product labeling and Medication Guide are finalized and will be provided to FDA before the surveys are administered. The protocol will include the sample size and confidence intervals associated with that sample size, how the sample will be selected, specific selection criteria, how the participants will be recruited, how and when the surveys will be administered, and an explanation of the design features included to minimize bias. A copy of the survey questionnaire will be included with the protocol.

9.4.2 Program Monitoring, Analysis and Reporting

9.4.2.1 Safety Surveillance

The activities occurring under the REMS will be integrated with the pharmacovigilance program to ensure proper surveillance, monitoring, and reporting of adverse events. Adverse event reports will be individually reviewed and evaluated in aggregate to determine if changes to the REMS education could help to further mitigate the risks.

Periodic safety assessments will include the following information in addition to assessment of those risk areas highlighted earlier:

1. Overdose.
2. Inappropriate prescribing and medication errors.
3. Accidental exposures, including asymptomatic reports in children and adults.
4. Drug-drug interactions.

9.4.2.2 REMS Reporting

The REMS assessment will include the following:

- A summary of all changes to the Contrave REMS that were implemented during the reporting period.
- A report of periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR §208.24.
- An assessment of HCP and patient understanding of the safe use of Contrave (the results of KAB surveys administered to prescribers and patients).
- Based on the information provided, an assessment and conclusion of whether the Contrave REMS is meeting its goals and whether modifications to the program are needed.
- Cross-reference to safety assessments described above.

9.4.2.3 Utilization Patterns

Pharmacy benefit claims will be gathered systematically and evaluated for Contrave utilization patterns. Established methodology exists to leverage large pharmacy-benefit manager (PBM) databases to ascertain real world utilization of Contrave (Steinkellner, 2010; Chang, 2010). Using these claims databases, a prospective cohort will be identified and followed specifically to determine adherence to labeling. Upon identifying patients filling an initial prescription for Contrave, consent will be sought for enrollment in a prospective

cohort of patients that will be contacted on a regular basis. Key information collected will include:

- Patient demographics and clinical characteristics, including height and body weight.
- Frequency of blood pressure assessments by healthcare providers.
- Persistence of Contrave therapy and adherence to the treatment algorithm.

9.4.2.4 Proposed Intervention to Potential Non-Compliance or Potential Signals

The education program will be evaluated in the context of the performance of the entire REMS program to determine the extent to which the REMS is meeting the goals and objectives of the REMS and whether or not the goals, objectives, or the education program should be modified.

Should one or more of the REMS component tools be shown to be ineffective, a revision to the specified REMS tool will be submitted to FDA prior to implementing any changes to the approved REMS.

9.5 Clinical Outcomes Assessment

The NB clinical development program was designed to address regulatory guidance on the development of products for weight management. The program primarily evaluated surrogate measures of both potential benefit (e.g., weight reduction and improved HDL, HbA1c, hs-CRP) and potential risk (e.g., increases from placebo in blood pressure and heart rate). Results from the NB clinical program, along with extensive clinical experience with the individual constituent agents, provide evidence supporting a favorable benefit-risk profile of NB. The risks noted in the clinical development program can be managed in real world clinical practice through labeling and risk management measures. The potential impact of NB on cardiovascular outcomes will be more definitively addressed with additional data obtained post approval; potential approaches to obtain such data are outlined below.

The patient population utilizing obesity pharmacotherapy is predominantly female, Caucasian, with an average age in the mid-40s. As a result, major adverse cardiovascular events (MACE) occur rarely. Based on clinical trials and literature reports, rates of MACE in the obese population intended for Contrave therapy are estimated to range between 0.1-0.3% per year. For example, data from over 14 years of follow-up of an obese cohort in the Nurse's Health Study revealed an annualized MACE rate among subjects with a BMI ≥29 of approximately 0.2% (Willett et al, 1995).

Assessing risk for MACE when the background rate is low presents significant challenges. A common approach to facilitate event collection involves conducting a study in an enriched, high-risk subset of the overall population intended for treatment. This approach is most valid when the results apply equally to the high risk group compared to the more general population. For example, the results of diabetes trials that enroll high CV risk patients are applicable because diabetes therapies are used by both patients at low and high CV risk. In contrast, obesity pharmacotherapy is not usually pursued for older, higher-risk patients (Table 51), and such a higher-risk population is not intended for Contrave. Therefore, results in a higher-risk group are unlikely to be as applicable to the population of interest.

An alternative approach is to enroll a large number of patients from the intended lower-risk population. This approach has the advantage of providing results that are directly applicable and relevant to real world use. The focus of such an investigation would be specific assessment of major cardiovascular events, such as myocardial infarction, stroke, acute revascularization and cardiovascular death. As previously noted, the low background rate necessitates a large sample size to reliably assess the frequency of these events, the exact sample size is dependent on the amount of excess risk to be ruled out.

Table 53 shows a range of sample sizes that could be considered for a large trial as that described above, based on the following assumptions: 1) a recruitment period of 2 years, 2) patient follow-up for a fixed period of 2 years, 3) a lost to follow-up rate of 2% per year, 4) a composite MACE endpoint annualized event rate of 0.15 to 0.25% in the control group, and 5) an underlying relative risk of active to control of 1. The sample sizes calculated provide at least 90% power to demonstrate that the upper bound of a one-sided 97.5% confidence interval for the relative risk would fall below the pre-specified non-inferiority margin.

Table 53 Sample Size Estimates for a Large Trial in a Low-CV Risk Obese Population

Parameter									
Annualized Event Rate	0.15%			0.2%			0.25%		
Non-inferiority Margin based on Relative Risk	2	2.5	3	2	2.5	3	2	2.5	3
Relative Risk Difference Under H_0	0.15%	0.225%	0.3%	0.2%	0.3%	0.4%	0.25%	0.375%	0.5%
Excess events that can be ruled out per 1000 patients treated	1.5	2.25	3	2	3	4	2.5	3.75	5
Total Sample Size	59,160	33,854	23,550	44,384	25,400	17,668	35,520	20,326	14,140

With these considerations in mind, two alternative approaches for gathering large samples are being evaluated:

- A randomized interventional trial
- A prospective, longitudinal, comparative cohort

9.5.1 Randomized Interventional Trial

The randomized, controlled trial (RCT) is the gold standard for addressing most clinical outcome questions. A Large Simple Trial (LST) is a type of RCT in which patients are evaluated and randomized at typical clinical practice settings using a limited number of specific research procedures, and with limited data collection focused on critical outcomes. These studies typically use adjudicated cardiovascular endpoints as primary outcomes and have helped determine the relative benefits and risks of treatments for hypertension and acute myocardial infarction, among others.

Strengths of an LST approach include:

- Randomized design minimizes selection bias and increases ability to detect small to moderate treatment effects and risks.

- Large sample size provides adequate power to detect small to moderate treatment effects and risks.
- Streamlined design and the general clinical practice setting enable enrollment of large numbers of patients.
- Minimization of exclusion criteria and study procedures increases the feasibility and applicability of trial results to the intended real-world patient population.

Challenges in studying a large population of obese patients may include:

- Randomized treatment assignment to a placebo or non-drug control may discourage enrollment and long-term participation, and may delay the accrual of sufficient data for timely evaluation.
- Early or imbalanced discontinuations from randomized treatments and cross-over between treatment groups will bias results toward demonstration of apparent equivalence.

9.5.2 Prospective Cohort Study

Established methodology exists to leverage large pharmacy-benefit manager (PBM) databases to enroll a large, prospective sample of Contrave patients in a real-world setting. Patients presenting to a pharmacy with an initial Contrave prescription can be asked to participate in a prospective cohort, and data can be gathered through frequent patient contact as well as pharmacy data. Key information obtained via self report, pharmacy database, or medical records could include:

- Demographics and clinical characteristics, including height and bodyweight.
- Frequency of blood pressure measurements by healthcare providers.
- Persistence of Contrave therapy and adherence to the treatment algorithm included in labeling.
- Hospitalizations and data related to cardiovascular and other key clinical events.

A subset of randomly selected cohort patients can have self-reported and pharmacy data validated by in-home study visits conducted by trained nursing staff. Outcome data would be independently adjudicated. Cohort patients would be followed regardless of persistence on Contrave therapy.

Several strategies can be considered to establish an appropriate control group and assess relative risk of Contrave therapy, including an epidemiologically matched cohort, possibly patients on other obesity pharmacotherapy, or a historical control.

Strengths of the prospective cohort approach include:

- Ability to rapidly capture data for a large, representative, and real-world patient population in a timely manner.
- Ability to implement simultaneously with product launch, enabling rapid enrollment and early data generation.
- Open label design allows for ongoing data analysis and risk assessment.
- Patients recruited would be very representative of naturalistic use, as study participation is not a barrier to or modification of usual care.

- Data on how the product is being utilized, adherence to treatment guidelines, and REMS effectiveness would also be obtained.

Limitations of the prospective cohort approach include:

- The non-randomized nature of the control group potentially confounds the evaluation of spontaneous events that are only modestly increased with treatment. Specifically, small increases in risk may not be definitively ruled out.
- Naturalistic use may be associated with limited treatment duration, high rates of early treatment discontinuation or treatment cross-over.
- The need for a substantially large sample size to minimize the impact of the other noted limitations.

As large PBMs process the majority of prescriptions filled in the US, it is anticipated that up to 10% of all initial prescriptions can be enrolled in a prospective cohort. Under that scenario, and based on reasonable estimates of commercial utilization, several tens of thousands of patients would be enrolled over the first two years of marketing.

In summary, in addition to choosing between a prospective LST or cohort approach to address the question of clinical outcomes with Contrave therapy, a number of other study design issues remain. Orexigen has engaged an external advisory group from academia and industry to further develop appropriate plans. Orexigen intends to discuss these issues with FDA and reach agreement on an appropriate and feasible approach to a definitive and timely investigation of cardiovascular outcomes with Contrave use.

10 BENEFIT – RISK EVALUATION

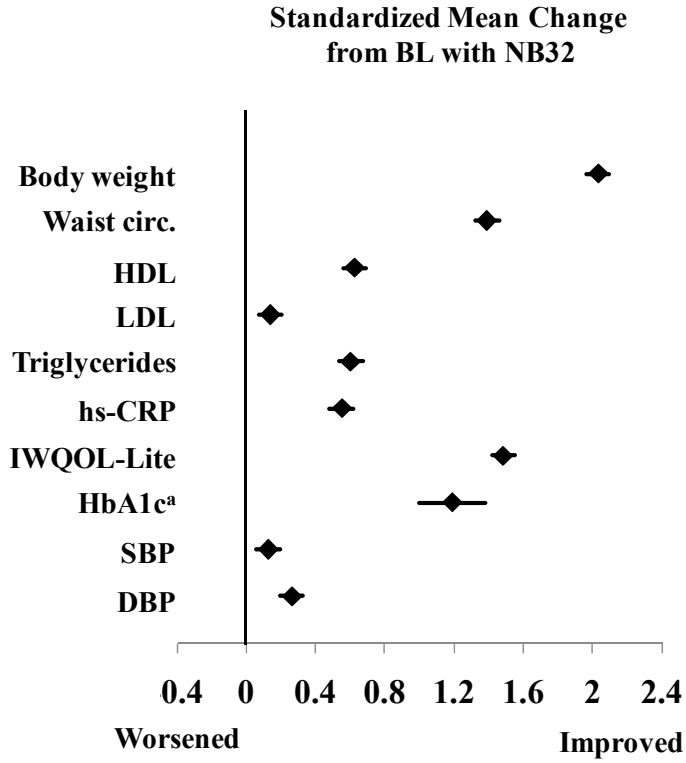
The key benefits of NB treatment in obese/overweight patients receiving a range of behavioral modification/diet and exercise counseling include clinically meaningful and sustained weight loss in a substantial number of patients, together with improvements in a variety of cardiometabolic endpoints thought to be reflective of longer-term cardiovascular outcome. Additional benefits are seen in patient self-reported measures of quality of life and exploratory measures indicating that patients may be better able to control eating. As such, NB exhibits many of the characteristics of an efficacious weight loss agent as described in FDA guidance. The benefits of NB treatment are summarized in more detail below:

- Clinically meaningful weight loss was apparent early in treatment. Weight loss was sustained, and those patients who continued treatment through 56 weeks experienced the most substantial weight loss.
- The efficacy of NB was observed across all demographic and clinical subgroups evaluated, including patients with hypertension, dyslipidemia, history of cardiovascular disease, type 2 diabetes, impaired fasting glucose, or history of depression.
- Significant effects of NB treatment were observed on a number of weight-related cardiometabolic parameters (e.g., waist circumference, triglycerides, HDL-cholesterol, and hs-CRP); HDL increases and triglyceride reductions were observed irrespective of history of dyslipidemia or treatment for this condition.
- Patients with type 2 diabetes benefitted from weight loss, improvements in waist circumference, HDL, triglycerides, and glycemic control (particularly decreased HbA1c). A lower proportion of NB-treated patients required adjustments to their antidiabetic medications due to poor glycemic control.
- Greater proportions of NB-treated patients reported clinically meaningful improvements in weight-related quality of life compared with placebo, providing further evidence of the range of clinical benefits that can be derived from NB treatment.
- Greater effects of NB treatment were observed on multiple items of the COE questionnaire relative to placebo, indicating greater control of eating with NB treatment.

The risk mitigation strategy places emphasis on patient selection and management according to the treatment algorithm in Figure 36. One major goal of the program is to encourage long-term therapy only in patients who achieve adequate weight loss response after a 4-month therapeutic trial. It is therefore pertinent to consider the benefit in this subgroup of patients. The observed benefits in patients achieving ≥5% response is shown in Figure 39.

In this patient subgroup, improvements from baseline are evident across all secondary cardiometabolic endpoints including blood pressure for both NB and placebo, with a greater proportion of NB than placebo patients (53% vs. 21%) achieving this level of weight loss.

Figure 39 Summary of Key Efficacy Endpoints Among 5% Weight Loss Responders in the Pooled Phase 3 Studies (mITT-LOCF)



	NB32 N=1085	Placebo N=274
	LS Mean Change from BL	
Body weight	-12.1%	-10.4%
Waist circ.	-10.1 cm	-8.3 cm
HDL	5.3 mg/dL	2.4 mg/dL
LDL	-3.3 mg/dL	-0.8 mg/dL
Triglycerides	-18.1%	-10.9%
hs-CRP	-38.4%	-40.7%
IWQOL-Lite	14.6	12.9
HbA1c[a]	-1.0%	-0.5%
SBP	-1.2 mm Hg	-3.9 mm Hg
DBP	-1.8 mm Hg	-3.4 mm Hg
	Proportion w/ ≥5% weight loss	
	53% (1085/2043)	21% (274/1319)

[a] HbA1c is for NB-304 only; Data are in left panel are standardized mean change from BL with NB32 and associated 95% CI.
Abbreviations: BL=baseline; circ=circumference; DBP=diastolic blood pressure; HDL=high-density lipoproteins; HbA1c=hemoglobin A1c; hs-CRP=high sensitivity C reactive protein; IWQOL=Impact of Weight on Quality of Life; LDL=low-density lipoproteins; LS mean=least squares mean; SBP=systolic blood pressure.

The benefits of NB treatment are counterbalanced with generally well-understood risks, in particular the observed mild pressor effect and seizures, which stem from the bupropion component of NB. As described in the context of risk mitigation, these risks are manageable through proper patient selection, adherence to labeling instructions, and diligent monitoring for clinically significant weight loss and early indications that patients may be at an increased risk not evident prior to treatment initiation. In this context, patients who exhibit ≥5% weight loss earlier in their treatment trial are not only likely to benefit the most, but are expected to have risks related to the bupropion pressor effect at least partially mitigated. Key safety findings from the NB development program include the following:

- The use of NB was generally well-tolerated, with the frequency and distribution of safety findings being consistent with the established profiles for naltrexone and bupropion.
- Common AEs such as nausea and vomiting tended to occur early in treatment (during the dose-escalation phase), were mostly mild to moderate in severity, and were generally self-limiting.

- The incidence of treatment-emergent SAEs overall was low (generally <0.1% for any given event), and with the exception of cholecystitis/cholelithiasis events, equally distributed across treatment groups; the vast majority of SAEs in NB-treated patients were considered unrelated to study drug.
- Initiation of treatment with NB was associated with transient increases from baseline of approximately 1 mm Hg in mean blood pressure followed by small reductions below baseline. These early increases are consistent with the known hemodynamic effects of bupropion and were attenuated by weight loss in patients who responded to therapy. The small elevations in heart rate seen with NB treatment are also consistent with known bupropion effects.
- The hemodynamic effects of NB are due to bupropion. Bupropion has been extensively prescribed since its original approval more than 20 years ago, and has a long history of safe use even in populations considered at risk for CV disease.
- The incidence of major cardiovascular events (cardiovascular death, myocardial infarction and cerebrovascular accident) and revascularization procedures were low and comparable between NB- and placebo-treated patients, although the number of events is too low to draw firm conclusions.
- Seizures occurred infrequently at a rate that is consistent with that observed for approved doses of bupropion SR.
- Treatment with NB in the target patient population does not appear to be associated with an increased risk for depression or suicidality.
- No hepatotoxicity was observed with long-term NB treatment.
- Clinical laboratory evaluations were generally unremarkable, and values outside of normal ranges tended to be sporadic and unrelated to dose.
- Neither bupropion nor naltrexone has historically been associated with prolongation of QTc intervals, and review of QT, QTc and the other ECG parameters in patients during long-term NB treatment revealed no noteworthy findings.

Weight loss is generally associated with decreases in mean blood pressure; while this effect was observed for both NB and placebo patients it was greater for placebo. Endpoint values for blood pressure were either unchanged or decreased relative to baseline with NB treatment. In addition, NB patients who lost at least 5% of their initial body weight had reductions from baseline in mean blood pressure.

To better understand the risk of a pressor effect relative to the benefit of weight loss with NB, an analysis was conducted on the pooled phase 3 trials to assess how many patients would need to be treated with NB to achieve a ≥5% weight loss, namely the number needed to treat (NNT: 3). Similarly, assessment of how many patients would need to be treated to elicit a defined outlier increases in SBP, DBP or heart rate (≥10 mm Hg increase in SBP or DBP or a ≥10 bpm increase in heart rate for at least 2 consecutive measurements) was performed, namely the number needed to harm (NNH: 13). Calculation of the likelihood to be helped or harmed (LHH) is based on the ratio of NNH to NNT. While matching up of correct benefit and harm measures for an individual patient is subjective, LHH methodology permits quantification of opposing effects of therapy (Citrome 2010). For these weight loss and blood

pressure/heart rate outliers, the LHH is 4, meaning that patients treated with NB are approximately 4 times more likely to achieve ≥5% weight loss than one of the defined outlier increases in SBP, DBP or heart rate.

The known risks associated with NB treatment (in particular the pressor effect, seizures, and suicidality) will be readily managed via implementation of risk mitigation steps, including a REMS, focused launch strategy, and post-approval studies and data collection. Key features of this program will include appropriate product labeling, a Medication Guide, and a comprehensive communication plan. An important aspect of the REMS will be educating prescribers on the importance of appropriate patient selection and clinical management. Appropriate candidates for NB will include male and female patients with a BMI ≥30 or ≥27 kg/m^2 with accompanying comorbidities who are motivated to adhere to healthier lifestyle choices. Inappropriate candidates will include patients with a BMI <27 kg/m^2, adolescents, patients not motivated to change lifestyle choices, chronic opioid users, patients at risk for seizures, and patients with significant cardiovascular risks. NB should be used with caution in patients with hypertension, a history of cardiovascular disease or of psychiatric disorders, and when administered concomitantly with agents that are known to decrease seizure threshold or increase blood pressure.

Because both components of NB have been individually used for over 20 years, it is unlikely that unforeseen risks will emerge as a result of the use of NB. Nonetheless, routine pharmacovigilance with targeted surveillance and data collection for events of interest, as well as the use of frequently assessed risk mitigation tools, will allow Orexigen to monitor for and manage any unforeseen risks that could potentially occur. In addition to the REMS elements and pharmacovigilance activities outlined above, Orexigen is developing a plan for additional clinical studies to assess: 1) prescription utilization patterns, 2) physician and patient adherence to labeling, and 3) the impact of Contrave on cardiovascular outcomes. Discussion of study options with FDA is anticipated prior to the Advisory Committee.

In summary, the benefits of NB outweigh the risks given the sustained and clinically meaningful weight loss and improvement in many markers of cardiometabolic risk and patient-reported quality of life. These benefits in aggregate are expected to be greater in general clinical practice, as proposed labeling would lead to discontinuation of treatment for patients not experiencing at least a 5% decrease from baseline in body weight. Benefits are observed across a range of overweight and obese patient subgroups and in various treatment settings. Of note, the population of patients receiving currently approved bupropion containing therapies has important similarities to patients enrolled in the NB clinical program, as well as the population of patients who receive currently marketed obesity pharmacotherapy. In addition, clinical experience and investigation in relevant patient populations, including those with cardiovascular risk factors or established cardiovascular disease, have not identified specific safety signals for clinical cardiovascular events. Thus, the safety profile is well-understood, with known risks that are predictable and manageable via appropriate risk mitigation approaches. Given the growing epidemic of obesity, availability of NB could provide a useful tool for physicians and patients who are currently challenged with very limited pharmacotherapeutic options.

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12 LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
AERS	Adverse Event Reporting System
alpha-MSH	Alpha-melanocyte stimulating hormone
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
AUP	Appropriate use program
BA	Bioavailability
BE	Bioequivalence
BID	Twice daily
BL	Baseline
BMI	Body mass index
BOCF	Baseline observation carried forward
bpm	Beats per minute
BUN	Blood urea nitrogen
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CHF	Congestive heart failure
CI	Confidence interval
CK-MB	Creatine kinase isoenzyme MB
C_{max}	Maximum plasma concentration
COE	Control of Eating
CPK	Creatine phosphokinase
CT	Computed tomography
CTP	Closed testing procedure
CV	Cardiovascular
CVA	Cerebrovascular accident
CYP	Cytochrome P450

12 LIST OF ABBREVIATIONS (*Continued*)

DA	Dopamine
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DEXA	Dual energy x-ray absorptiometry
DMEP	Division of Metabolism and Endocrinology Products
ECG	Electrocardiogram
EEG	Electroencephalogram
E_{max}	Maximum efficacy
EMS	Emergency medical service
FCI	Food Craving Inventory
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HbA1c	Hemoglobin A1c
HCl	Hydrochloride
HCP	Healthcare professional
HDL	High-density lipoprotein
hERG	Human ether-a-go-go related gene
HOMA-IR	Homeostasis model assessment of insulin resistance
HRQoL	Health-related quality of life
hs-CRP	High-sensitivity C reactive protein
IDS-SR	Inventory of Depressive Symptomatology-Self Reported
iKr	Delayed rectifier K+ current
IP	Intraperitoneal
IR	Immediate release
ITT	Intent-to-treat
ITT-MMRM	Intent-to-treat - mixed effect model of repeated measures
IWQOL	Impact of Weight on Quality of Life
KAB	Knowledge, Attitude, Behavior
LDL	Low-density lipoprotein
LHH	Likelihood to be helped or harmed

12 LIST OF ABBREVIATIONS (*Continued*)

LOCF	Last observation carried forward
LS	Least squares
LST	Large Simple Trials
MACE	Major adverse cardiovascular events
MADRS	Montgomery-Asberg Depression Rating Scale
MC4	Hypothalamic melanocortin 4 receptors
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MRA	Magnetic resonance angiography
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
NB	Naltrexone and bupropion in combination
NB16	Naltrexone SR 16 mg/bupropion SR 360 mg or 400
NB32	Naltrexone SR 32 mg/bupropion SR 360 mg or 400
NB48	Naltrexone SR 48 mg/bupropion SR 360 mg or 400
NB50	Naltrexone SR 50 mg/bupropion SR 300 mg or 400
NB48/50	Includes both dose levels (naltrexone SR 48 mg/bupropion SR 360 mg and naltrexone SR 50 mg/bupropion SR 300 mg)
NDA	New Drug Application
NE	Norepinephrine
NHLBI	National Heart, Lung, and Blood Institute
NNH	Number needed to harm
NNT	Number needed to treat
NOS	Not otherwise specified
NPY/AgRP	Neuropeptide Y/Agouti-related peptide
OCT2	Organic Cation Transporter
PBM	Pharmacy-benefit manager
PCS	Potentially clinically significant
PD	Pharmacodynamics
PI	Prescribing information

12 LIST OF ABBREVIATIONS (*Continued*)

PK	Pharmacokinetics
POMC	Hypothalamic pro-opiomelanocortin
QTc	Corrected QT interval of ECG
QTcF	Corrected QT interval by the method of Fridericia
RCT	Randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategies
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SMQ	Standard MedDRA Queries
SOC	System organ class
SR	Sustained release
SSRI	Selective serotonin re-uptake inhibitor
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
TME	Targeted medical event
Total NB	All doses of combination naltrexone and bupropion treatment
ULN	Upper limit of normal
U.S.	United States
VTA	Ventral tegmental area
WHO	World Health Organization
XL	Extended release

13 APPENDICES

Appendix 1 Prescribing information for Wellbutrin SR® (bupropion HCl) and ReVia® (naltrexone HCl)

PRESCRIBING INFORMATION

WELLBUTRIN SR®
(bupropion hydrochloride)
Sustained-Release Tablets

WARNING
Suicidality and Antidepressant Drugs

Use in Treating Psychiatric Disorders: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN SR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. WELLBUTRIN SR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

Use in Smoking Cessation Treatment: WELLBUTRIN®, WELLBUTRIN SR®, and WELLBUTRIN XL® are not approved for smoking cessation treatment, but bupropion under the name ZYBAN® is approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke.

All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking ZYBAN in the postmarketing experience. When symptoms were reported, most were during treatment with ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced

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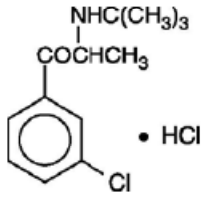
worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of ZYBAN.

Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (See WARNINGS: Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment and PRECAUTIONS: Information for Patients.)

DESCRIPTION

WELLBUTRIN SR (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO{\bullet}HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



WELLBUTRIN SR is supplied for oral administration as 100-mg (blue), 150-mg (purple), and 200-mg (light pink), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40 Lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of serotonin. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics: Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days. In a study comparing chronic dosing with WELLBUTRIN SR 150 mg twice daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, peak plasma concentrations of bupropion at steady state for WELLBUTRIN SR were approximately 85% of those achieved with the immediate-release formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all 3 of the detectable bupropion metabolites. Thus, at steady state, WELLBUTRIN SR, given twice daily, and the immediate-release formulation of bupropion, given 3 times daily, are essentially bioequivalent for both bupropion and the 3 quantitatively important metabolites.

Absorption: Following oral administration of WELLBUTRIN SR to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased C_{max} and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect.

Distribution: In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism: Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by or which inhibit/induce the cytochrome P450IIB6 (CYP2B6) isoenzyme, such as ritonavir. In a healthy volunteer study, ritonavir at a dose of 100 mg twice daily reduced the AUC and C_{max} of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

In a second healthy volunteer study, ritonavir at a dose of 600 mg twice daily decreased the AUC and the C_{max} of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%.

In another healthy volunteer study, KALETRA® (lopinavir 400 mg/ritonavir 100 mg twice daily) decreased bupropion AUC and C_{max} by 57%. The AUC and C_{max} of hydroxybupropion were decreased by 50% and 31%, respectively (see PRECAUTIONS: Drug Interactions).

Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is coadministered with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of WELLBUTRIN SR. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

Elimination: Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild-to-severe cirrhosis. The first study showed that the half-life of

hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild-to-moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in patients with mild-to-moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. A second study, comparing normal subjects and patients with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL/min) showed that exposure to a single 150-mg dose of sustained-release bupropion was approximately 2-fold higher in patients with impaired renal function while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. The elimination of bupropion and/or the major metabolites of bupropion may be reduced by impaired renal function (see PRECAUTIONS: Renal Impairment).

Left Ventricular Dysfunction: During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy volunteers.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on

a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS: Geriatric Use).

Gender: A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

CLINICAL TRIALS

The efficacy of the immediate-release formulation of bupropion as a treatment for depression was established in two 4-week, placebo-controlled trials in adult inpatients with depression and in one 6-week, placebo-controlled trial in adult outpatients with depression. In the first study, patients were titrated in a bupropion dose range of 300 to 600 mg/day on a 3 times daily schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from that scale, and the Clinical Global Impressions (CGI) severity score. A second study included 2 fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion, but only at the 450-mg/day dose; the results were positive for the HDRS total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the effectiveness of the immediate-release formulation of bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.

Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence of the immediate-release and sustained-release forms of bupropion under steady-state conditions, i.e., bupropion sustained-release 150 mg twice daily was shown to be bioequivalent to 100 mg 3 times daily of the immediate-release formulation of bupropion, with regard to both rate and extent of absorption, for parent drug and metabolites.

In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded during an 8-week open trial on WELLBUTRIN SR (150 mg

twice daily) were randomized to continuation of their same dose of WELLBUTRIN SR or placebo, for up to 44 weeks of observation for relapse. Response during the open phase was defined as CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse during the double-blind phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving continued treatment with WELLBUTRIN SR experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

INDICATIONS AND USAGE

WELLBUTRIN SR is indicated for the treatment of major depressive disorder.

The efficacy of bupropion in the treatment of a major depressive episode was established in two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of depressed outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of WELLBUTRIN SR in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use WELLBUTRIN SR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

WELLBUTRIN SR is contraindicated in patients with a seizure disorder.

WELLBUTRIN SR is contraindicated in patients treated with ZYBAN (bupropion hydrochloride) Sustained-Release Tablets; WELLBUTRIN (bupropion hydrochloride), the immediate-release formulation; WELLBUTRIN XL (bupropion hydrochloride), the extended-release formulation; or any other medications that contain bupropion because the incidence of seizure is dose dependent.

WELLBUTRIN SR is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

WELLBUTRIN SR is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of WELLBUTRIN SR and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with WELLBUTRIN SR.

WELLBUTRIN SR is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up WELLBUTRIN SR.

WARNINGS

Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for WELLBUTRIN SR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment: WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL are not approved for smoking cessation treatment, but bupropion under the name ZYBAN is approved for this use. Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation **(see BOXED WARNING, ADVERSE REACTIONS). These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.** Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke. When symptoms were reported, most were during bupropion treatment, but some were following discontinuation of bupropion therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. All patients being treated with bupropion as part of smoking cessation treatment should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness.

Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of ZYBAN.

Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as six months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and

depression. It should be noted that WELLBUTRIN SR is not approved for use in treating bipolar depression.

Bupropion-Containing Products: Patients should be made aware that WELLBUTRIN SR contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN SR should not be used in combination with ZYBAN, or any other medications that contain bupropion, such as WELLBUTRIN (bupropion hydrochloride), the immediate-release formulation or WELLBUTRIN XL (bupropion hydrochloride), the extended-release formulation.

Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with WELLBUTRIN SR. WELLBUTRIN SR should be discontinued and not restarted in patients who experience a seizure while on treatment.

- **Dose: At doses of WELLBUTRIN SR up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1,000) at the maximum recommended dose of 400 mg/day.**

  Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. The 450-mg/day upper limit of this dose range is close to the currently recommended maximum dose of 400 mg/day for WELLBUTRIN SR. This seizure incidence (0.4%) may exceed that of other marketed antidepressants and WELLBUTRIN SR up to 300 mg/day by as much as 4-fold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted.

  Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day, which is twice the usual adult dose and one and one-half the maximum recommended daily dose (400 mg) of WELLBUTRIN SR. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

  Data for WELLBUTRIN SR revealed a seizure incidence of approximately 0.1% (i.e., 3 of 3,100 patients followed prospectively) in patients treated at doses in a range of 100 to 300 mg/day. It is not possible to know if the lower seizure incidence observed in this study involving the sustained-release formulation of bupropion resulted from the different formulation or the lower dose used. However, as noted above, the immediate-release and sustained-release formulations are bioequivalent with regard to both rate and extent of absorption during steady state (the most pertinent condition to estimating seizure incidence), since most observed seizures occur under steady-state conditions.

- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, 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.**

Recommendations for Reducing the Risk of Seizure: **Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if**

- **the total daily dose of WELLBUTRIN SR does *not* exceed 400 mg,**
- **the daily dose is administered twice daily, and**
- **the rate of incrementation of dose is gradual.**
- **No single dose should exceed 200 mg to avoid high peak concentrations of bupropion and/or its metabolites.**

WELLBUTRIN SR should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

Hepatic Impairment: WELLBUTRIN SR should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 100 mg every day or 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS

General: *Agitation and Insomnia:* Patients in placebo-controlled trials with WELLBUTRIN SR experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials

Adverse Event Term	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Depressed patients treated with an immediate-release formulation of bupropion or with WELLBUTRIN SR have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. WELLBUTRIN SR is expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies, patients experienced weight gain or weight loss as shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials

Weight Change	WELLBUTRIN SR 300 mg/day (n = 339)	WELLBUTRIN SR 400 mg/day (n = 112)	Placebo (n = 347)
Gained >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of WELLBUTRIN SR should be considered.

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. A patient should stop taking WELLBUTRIN SR and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

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.

Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of WELLBUTRIN SR Tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

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

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients

with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. A second study, comparing normal subjects and patients with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL/min) showed that exposure to a single 150-mg dose of sustained-release bupropion was approximately 2-fold higher in patients with impaired renal function while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. WELLBUTRIN SR 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 usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with WELLBUTRIN SR and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions," "Quitting Smoking, Quit-Smoking Medication, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions," and "What Other Important Information Should I Know About WELLBUTRIN SR?" is available for WELLBUTRIN SR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking WELLBUTRIN SR.

Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment: Although WELLBUTRIN SR is not indicated for smoking cessation treatment, it

contains the same active ingredient as ZYBAN which is approved for this use. Patients should be informed that quitting smoking, with or without ZYBAN, may be associated with nicotine withdrawal symptoms (including depression or agitation), or exacerbation of pre-existing psychiatric illness. Furthermore, some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to report these symptoms to their healthcare provider immediately.

Bupropion-Containing Products: Patients should be made aware that WELLBUTRIN SR contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN SR should not be used in combination with ZYBAN or any other medications that contain bupropion hydrochloride (such as WELLBUTRIN, the immediate-release formulation and WELLBUTRIN XL, the extended-release formulation).

As dose is increased during initial titration to doses above 150 mg/day, patients should be instructed to take WELLBUTRIN SR in 2 divided doses, preferably with at least 8 hours between successive doses, to minimize the risk of seizures.

Patients should be told that WELLBUTRIN SR should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS-active drug like WELLBUTRIN SR may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that WELLBUTRIN SR does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with WELLBUTRIN SR. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because WELLBUTRIN SR and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to swallow WELLBUTRIN SR tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets, as this may lead to an increased risk of adverse effects, including seizures.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: Few systemic data have been collected on the metabolism of bupropion following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion on the metabolism of other drugs.

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 WELLBUTRIN SR and drugs that are substrates of or inhibitors/inducers of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel). In addition, 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. The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg WELLBUTRIN SR tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir 400 mg (KALETRA) twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20% to 80%. This effect is thought to be due to the induction of bupropion metabolism. Patients receiving ritonavir may need increased doses of bupropion, but the maximum recommended dose of bupropion should not be exceeded (see CLINICAL PHARMACOLOGY: Metabolism).

While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).

Multiple oral doses of bupropion had no statistically significant effects on the single-dose pharmacokinetics of lamotrigine in 12 healthy volunteers.

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

Drugs Metabolized By Cytochrome P450IID6 (CYP2D6): Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a study of 15 male subjects (aged 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of

approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally 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.

Although citalopram is not primarily metabolized by CYP2D6, in one study bupropion increased the C_{max} and AUC of citalopram by 30% and 40%, respectively. Citalopram did not affect the pharmacokinetics of bupropion and its 3 metabolites.

MAO Inhibitors: Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Levodopa and Amantadine: Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of WELLBUTRIN SR to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Drugs That Lower Seizure Threshold: Concurrent administration of WELLBUTRIN SR and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.

Nicotine Transdermal System: (see PRECAUTIONS: Cardiovascular Effects).

Alcohol: 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 WELLBUTRIN SR. The consumption of alcohol during treatment with WELLBUTRIN SR should be minimized or avoided (also see CONTRAINDICATIONS).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m^2 basis); 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.

A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. In studies conducted in rats and rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively (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 300 mg/kg/day (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 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. WELLBUTRIN SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of WELLBUTRIN SR on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from WELLBUTRIN SR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders). Anyone considering the use of WELLBUTRIN SR in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use: Of the approximately 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No

overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

(See also WARNINGS and PRECAUTIONS.)

The information included under the Incidence in Controlled Trials subsection of ADVERSE REACTIONS is based primarily on data from controlled clinical trials with WELLBUTRIN SR. Information on additional adverse events associated with the sustained-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).

Incidence in Controlled Trials With WELLBUTRIN SR: ***Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With WELLBUTRIN SR:*** In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 or 400 mg/day of WELLBUTRIN SR and at a rate at least twice the placebo rate are listed in Table 4.

Table 4. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials

Adverse Event Term	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With WELLBUTRIN SR: Table 5 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of WELLBUTRIN SR and with placebo in placebo-controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of WELLBUTRIN SR is provided in the WARNINGS and PRECAUTIONS sections.

Table 5. Treatment-Emergent Adverse Events in Placebo-Controlled Trials[a]

Body System/ Adverse Event	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%

Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage[b]	0%	2%	—
Urinary tract infection	1%	0%	—

[a] Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of WELLBUTRIN SR, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

[b] Incidence based on the number of female patients.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials: Adverse events from Table 5 occurring in at least 5% of patients treated with WELLBUTRIN SR and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

WELLBUTRIN SR 300 mg/day: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

WELLBUTRIN SR 400 mg/day: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with WELLBUTRIN SR (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 2 through 5, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with WELLBUTRIN SR is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aggression, aphasia, coma, completed suicide, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, increased intraocular pressure, and mydriasis.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Bupropion is not a controlled substance.

Humans: Controlled clinical studies of bupropion (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs.

Animals: Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

OVERDOSAGE

Human Overdose Experience: Overdoses of up to 30 g or more of bupropion have been reported. Seizure was reported in approximately one-third of all cases. 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.

Overdosage Management: Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first

48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended.

Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.

Due to the dose-related risk of seizures with WELLBUTRIN SR, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

General Dosing Considerations: It is particularly important to administer WELLBUTRIN SR in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. WELLBUTRIN SR should be swallowed whole and not crushed, divided, or chewed, as this may lead to an increased risk of adverse effects including seizures.

Initial Treatment: The usual adult target dose for WELLBUTRIN SR is 300 mg/day, given as 150 mg twice daily. Dosing with WELLBUTRIN SR should begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as 150 mg twice daily, may be made as early as day 4 of dosing. There should be an interval of at least 8 hours between successive doses.

Increasing the Dosage Above 300 mg/day: As with other antidepressants, the full antidepressant effect of WELLBUTRIN SR may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 400 mg/day, given as 200 mg twice daily, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance Treatment: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In a study in which patients with major depressive disorder, recurrent type, who had responded during 8 weeks of acute treatment with WELLBUTRIN SR were assigned randomly to placebo or to the same dose of WELLBUTRIN SR (150 mg twice daily) during 44 weeks of

maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated (see CLINICAL TRIALS under CLINICAL PHARMACOLOGY). Based on these limited data, it is unknown whether or not the dose of WELLBUTRIN SR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Dosage Adjustment for Patients with Impaired Hepatic Function: WELLBUTRIN SR should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 100 mg every day or 150 mg every other day in these patients. WELLBUTRIN SR 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 (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

Dosage Adjustment for Patients with Impaired Renal Function: WELLBUTRIN SR should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

WELLBUTRIN SR Sustained-Release Tablets, 100 mg of bupropion hydrochloride, are blue, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 100" in bottles of 60 (NDC 0173-0947-55) tablets.

WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of 60 (NDC 0173-0135-55) tablets.

WELLBUTRIN SR Sustained-Release Tablets, 200 mg of bupropion hydrochloride, are light pink, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 200" in bottles of 60 (NDC 0173-0722-00) tablets.

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. Dispense in a tight, light-resistant container as defined in the USP.

Distributed by:
GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured by:
GlaxoSmithKline
Research Triangle Park, NC 27709
or DSM Pharmaceuticals, Inc.
Greenville, NC 27834

May 2010
WLS:5PI

MEDICATION GUIDE
WELLBUTRIN SR® (WELL byu-trin)
(bupropion hydrochloride) Sustained-Release Tablets

Read this Medication Guide carefully before you start using WELLBUTRIN SR and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about WELLBUTRIN SR, ask your doctor or pharmacist.

IMPORTANT: Be sure to read the three sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with medicines used to quit smoking; and the third section is entitled "What Other Important Information Should I Know About WELLBUTRIN SR?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

WELLBUTRIN SR has not been studied in children under the age of 18 and is not approved for use in children and teenagers.

Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with drugs used to quit smoking.

Although WELLBUTRIN SR is not a treatment for quitting smoking, it contains the same active ingredient (bupropion hydrochloride) as ZYBAN® which is used to help patients quit smoking.

Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or actions while taking bupropion to help them quit smoking. These symptoms can develop during treatment with bupropion or after stopping treatment with bupropion.

If you, your family member, or your caregiver notice agitation, hostility, depression, or changes in thinking or behavior that are not typical for you, or you have any of the following symptoms, stop taking bupropion and call your healthcare provider right away:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (ma
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without bupropion, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Before taking bupropion, tell your healthcare provider if you have ever had depression or other mental illnesses. You should also tell your doctor about any symptoms you had during other times you tried to quit smoking, with or without bupropion.

What Other Important Information Should I Know About WELLBUTRIN SR?

- **Seizures: There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN SR, especially in people:**
  - with certain medical problems.
  - who take certain medicines.

  The chance of having seizures increases with higher doses of WELLBUTRIN SR. For more information, see the sections "Who should not take WELLBUTRIN SR?" and "What should I tell my doctor before using WELLBUTRIN SR?" Tell your doctor about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are using WELLBUTRIN SR unless your doctor has said it is okay to take them.**

  If you have a seizure while taking WELLBUTRIN SR, stop taking the tablets and call your doctor right away. Do not take WELLBUTRIN SR again if you have a seizure.

- **High blood pressure (hypertension). Some people get high blood pressure, that can be severe, while taking WELLBUTRIN SR.** The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking.
- **Severe allergic reactions. Some people have severe allergic reaction to WELLBUTRIN SR. Stop taking WELLBUTRIN SR and call your doctor right away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.
- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking WELLBUTRIN SR, including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your doctor.

What is WELLBUTRIN SR?
WELLBUTRIN SR is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take WELLBUTRIN SR?
Do not take WELLBUTRIN SR if you

- have or had a seizure disorder or epilepsy.
- **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN® Tablets or WELLBUTRIN XL® Extended-Release Tablets.** Bupropion is the same active ingredient that is in WELLBUTRIN SR.
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- have taken within the last 14 days medicine for depression called a monoamine oxidase inhibitor (MAOI), such as NARDIL® (phenelzine sulfate), PARNATE® (tranylcypromine sulfate), or MARPLAN® (isocarboxazid).
- have or had an eating disorder such as anorexia nervosa or bulimia.
- are allergic to the active ingredient in WELLBUTRIN SR, bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in WELLBUTRIN SR.

What should I tell my doctor before using WELLBUTRIN SR?
Tell your doctor if you have ever had depression, suicidal thoughts or actions, or other mental health problems. See "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions."

- **Tell your doctor about your other medical conditions including if you:**
  - **are pregnant or plan to become pregnant**. It is not known if WELLBUTRIN SR can harm your unborn baby.
  - **are breastfeeding**. WELLBUTRIN SR passes through your milk. It is not known if WELLBUTRIN SR can harm your baby.
  - **have liver problems,** especially cirrhosis of the liver.
  - have kidney problems.
  - have an eating disorder such as anorexia nervosa or bulimia.
  - have had a head injury.
  - have had a seizure (convulsion, fit).
  - have a tumor in your nervous system (brain or spine).
  - have had a heart attack, heart problems, or high blood pressure.
  - are a diabetic taking insulin or other medicines to control your blood sugar.
  - drink a lot of alcohol.
  - abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using WELLBUTRIN SR.

How should I take WELLBUTRIN SR?

- Take WELLBUTRIN SR exactly as prescribed by your doctor.
- **Do not chew, cut, or crush WELLBUTRIN SR tablets.** If you do, the medicine will be released into your body too quickly. If this happens you may be more likely to get side effects including seizures. You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take WELLBUTRIN SR at the same time each day.
- Take your doses of WELLBUTRIN SR at least 8 hours apart.
- You may take WELLBUTRIN SR with or without food.
- If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and take your next tablet at the regular time. **This is very important.** Too much WELLBUTRIN SR can increase your chance of having a seizure.
- If you take too much WELLBUTRIN SR, or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while using WELLBUTRIN SR unless your doctor has told you it is okay.**
- It may take several weeks for you to feel that WELLBUTRIN SR is working. Once you feel better, it is important to keep taking WELLBUTRIN SR exactly as directed by your doctor. Call your doctor if you do not feel WELLBUTRIN SR is working for you.
- Do not change your dose or stop taking WELLBUTRIN SR without talking with your doctor first.

What should I avoid while taking WELLBUTRIN SR?

- Do not drink a lot of alcohol while taking WELLBUTRIN SR. If you usually drink a lot of alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your chance of having seizures.
- Do not drive a car or use heavy machinery until you know how WELLBUTRIN SR affects you. WELLBUTRIN SR can impair your ability to perform these tasks.

What are possible side effects of WELLBUTRIN SR?

WELLBUTRIN SR can cause serious side effects. Read this entire Medication Guide for more information about these serious side effects.

The most common side effects of WELLBUTRIN SR are loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.

If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.

These are not all the side effects of WELLBUTRIN SR. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store WELLBUTRIN SR?

- Store WELLBUTRIN SR at room temperature. Store out of direct sunlight. Keep WELLBUTRIN SR in its tightly closed bottle.
- WELLBUTRIN SR tablets may have an odor.

General Information about WELLBUTRIN SR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WELLBUTRIN SR for a condition for which it was not prescribed. Do not give WELLBUTRIN SR to other people, even if they have the same symptoms you have. It may harm them. Keep WELLBUTRIN SR out of the reach of children.

This Medication Guide summarizes important information about WELLBUTRIN SR. For more information, talk with your doctor. You can ask your doctor or pharmacist for information about WELLBUTRIN SR that is written for health professionals.

What are the ingredients in WELLBUTRIN SR?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40 Lake. The tablets are printed with edible black ink.

R_x only

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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May 2010
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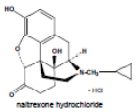
6557-00/December, 2001

REVIA®
(naltrexone hydrochloride tablets)

R_x only

DESCRIPTION: REVIA (naltrexone hydrochloride), an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. REVIA is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone.



naltrexone hydrochloride

REVIA is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL. REVIA is available in scored film-coated tablets containing 50 mg of naltrexone hydrochloride.

REVIA Tablets also contain: lactose, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80, yellow iron oxide and red iron oxide.

CLINICAL PHARMACOLOGY:

Pharmacodynamic Actions: REVIA is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids.

When co-administered with morphine, on a chronic basis, REVIA blocks the physical dependence to morphine, heroin and other opioids. REVIA has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of REVIA is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, REVIA will precipitate withdrawal symptomatology.

Clinical studies indicate that 50 mg of REVIA will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that doubling the dose of REVIA provides blockade for 48 hours, and tripling the dose of REVIA provides blockade for about 72 hours.

REVIA blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in experimental subjects.

The mechanism of action of REVIA in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. REVIA, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and REVIA has been shown to reduce alcohol consumption in clinical studies.

REVIA is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Pharmacokinetics: REVIA is a pure opioid receptor antagonist. Although well absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5 to 40%. The activity of naltrexone is believed to be due to both parent and the 6-ß-naltrexol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (53% to 79% of the dose), however, urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose and fecal excretion is a minor elimination pathway. The mean elimination half-life (T-1/2) values for naltrexone and 6-ß-naltrexol are 4 hours and 13 hours, respectively. Naltrexone and 6-ß-naltrexol are dose proportional in terms of AUC and Cmax over the range of 50 to 200 mg and do not accumulate after 100 mg daily doses.

Absorption: Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 98% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6-ß-naltrexol occur within one hour of dosing.

Distribution: The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 liters. *In vitro* tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range.

Metabolism: The systemic clearance (after intravenous administration) of naltrexone is ~3.5 L/min, which exceeds liver blood flow (~1.2 L/min). This suggests both that naltrexone is a highly extracted drug (>98% metabolized) and that extra-hepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6-ß-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-ß-naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products.

Elimination: The renal clearance for naltrexone ranges from 30-127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6-ß-naltrexol ranges from 230-369 ml/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-ß-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling.

Hepatic and Renal Impairment: Naltrexone appears to have extra-hepatic sites of drug metabolism and its major metabolite undergoes active tubular secretion (see **Metabolism** above). Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted (see **PRECAUTIONS: Special Risk Patients**).

Clinical Trials:

Alcoholism:

The efficacy of REVIA as an aid to the treatment of alcoholism was tested in placebo-controlled, outpatient, double blind trials. These studies used a dose of REVIA 50 mg once daily for 12 weeks as an adjunct to social and psychotherapeutic methods when given under conditions that enhanced patient compliance. Patients with psychosis, dementia, and secondary psychiatric diagnoses were excluded from these studies.

In one of these studies, 104 alcohol-dependent patients were randomized to receive either REVIA 50 mg once daily or placebo. In this study, REVIA proved superior to placebo in measures of drinking including abstention rates (51% vs. 23%), number of drinking days, and relapse (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving REVIA were shown to have lower relapse rates (21% vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo, but these results depended on the specific analysis used.

The clinical use of REVIA as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicenter safety study. This study of 865 individuals with alcoholism included patients with comorbid psychiatric conditions, concomitant medications, polysubstance abuse and HIV disease. Results of this study demonstrated that the side effect profile of REVIA appears to be similar in both alcoholic and opioid dependent populations, and that serious side effects are uncommon.

In the clinical studies, treatment with REVIA supported abstinence, prevented relapse and decreased alcohol consumption. In the uncontrolled study, the patterns of abstinence and relapse were similar to those observed in the controlled studies. REVIA was not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment.

Treatment of Opioid Addiction:

REVIA has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other non-opioid drugs of abuse.

There are no data that demonstrate an unequivocally beneficial effect of REVIA on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance.

The drug is reported to be of greatest use in good prognosis opioid addicts who take the drug as part of a comprehensive occupational rehabilitative program, behavioral contract, or other compliance-enhancing protocol. REVIA, unlike methadone or LAAM (levo-alpha-acetyl-methadol), does not reinforce medication compliance and is expected to have a therapeutic effect only when given under external conditions that support continued use of the medication.

Individualization of Dosage:

DO NOT ATTEMPT TREATMENT WITH REVIA UNLESS, IN THE MEDICAL JUDGEMENT OF THE PRESCRIBING PHYSICIAN, THERE IS NO REASONABLE POSSIBILITY OF OPIOID USE WITHIN THE PAST 7-10 DAYS. IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST.

Treatment of Alcoholism:

The placebo-controlled studies that demonstrated the efficacy of REVIA as an adjunctive treatment of alcoholism used a dose regimen of 50 mg/day. A flexible approach to a dosing regimen may be employed to enhance compliance. Thus, patients may receive 50 mg of REVIA (naltrexone hydrochloride) every weekday with a 100 mg dose on Saturday or patients may receive 100 mg every other day, or 150 mg every third day. Several of the clinical studies reported in the literature have employed the following dosing regimen: 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday. This dosing schedule appeared to be acceptable to many REVIA patients successfully maintaining their opioid-free state.

Experience with the supervised administration of a number of potentially hepatotoxic agents suggests that supervised administration and single doses of REVIA higher than 50 mg may have an associated increased risk of hepatocellular injury, even though three-times a week dosing has been well-tolerated in the addict population and in initial clinical trials in alcoholism. Clinics using this approach should balance the possible risks against the probable benefits and may wish to maintain a higher index of suspicion for drug-associated hepatitis and ensure patients are advised of the need to report non-specific abdominal complaints (see **PRECAUTIONS: Information for Patients**).

INDICATIONS AND USAGE: REVIA is indicated:

In the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.

REVIA has not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions.

CONTRAINDICATIONS: REVIA is contraindicated in:

1) Patients receiving opioid analgesics.
2) Patients currently dependent on opioids, including those currently maintained on opiate agonists [e.g., methadone or LAAM (levo-alpha-acetyl-methadol)].
3) Patients in acute opioid withdrawal (see **WARNINGS**).
4) Any individual who has failed the naloxone challenge test or who has a positive urine screen for opioids.
5) Any individual with a history of sensitivity to REVIA or any other components of this product. It is not known if there is any cross sensitivity with naloxone or the phenanthrene containing opioids.
6) Any individual with acute hepatitis or liver failure.

WARNINGS:

Hepatotoxicity:

REVIA has the capacity to cause hepatocellular injury when given in excessive doses.
REVIA 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 REVIA and the dose causing hepatic injury appears to be only five-fold or less. REVIA does not appear to be a hepatotoxin at the recommended doses.
Patients should be warned of the risk of hepatic injury and advised to stop the use of REVIA and seek medical attention if they experience symptoms of acute hepatitis.

Evidence of the hepatotoxic potential of REVIA is derived primarily from a placebo controlled study in which REVIA 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 20 REVIA 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 10 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 REVIA is a direct (i.e., not idiosyncratic) hepatotoxin.

This conclusion is also supported by evidence from other placebo controlled studies in which exposure to REVIA 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 patients with Alzheimer's Disease who received REVIA (at doses up to 300 mg/day) for 5 to 8 weeks in an open clinical trial have been reported.

Although no cases of hepatic failure due to REVIA administration have ever been reported, physicians are advised to consider this as a possible risk of treatment and to use the same care in prescribing REVIA as they would other drugs with the potential for causing hepatic injury.

Unintended Precipitation of Abstinence:

To prevent occurrence of an acute abstinence syndrome, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting REVIA. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of REVIA. The naloxone challenge test is described in the DOSAGE AND ADMINISTRATION section.

Attempt to Overcome Blockade:

While REVIA is a potent antagonist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by REVIA is surmountable. This is useful in patients who may require analgesia, but poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opiate blockade (see **PRECAUTIONS: Information for Patients**).

There is also the possibility that a patient who had been treated with naltrexone will respond to lower doses of opioids than previously used, particularly if taken in such a manner that high plasma concentrations remain in the body beyond the time that naltrexone exerts its therapeutic effects. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after naltrexone treatment is discontinued.

Ultra Rapid Opioid Withdrawal:

Safe use of REVIA in ultra rapid opiate detoxification programs has not been established (see **ADVERSE REACTIONS**).

PRECAUTIONS:

General:

When Reversal of REVIA Blockade is Required: In an emergency situation in patients receiving fully blocking doses of REVIA, a suggested plan of management is regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction) presumably due to histamine release.

Irrespective of the drug chosen to reverse REVIA blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Accidentally Precipitated Withdrawal: Severe opioid withdrawal syndromes precipitated by the accidental ingestion of REVIA have been reported in opioid-dependent individuals. Symptoms of withdrawal have usually appeared within five minutes of ingestion of REVIA and have lasted for up to 48 hours. Mental status changes including confusion, somnolence and visual hallucinations have occurred. Significant fluid losses from vomiting and diarrhea have required intravenous fluid administration. In all cases patients were closely monitored and therapy with non-opioid medications was tailored to meet individual requirements.

Use of REVIA does not eliminate or diminish withdrawal symptoms. If REVIA is initiated early in the abstinence process, it will not preclude the patient's experience of the full range of signs and symptoms that would be experienced if REVIA had not been started. Numerous adverse events are known to be associated with withdrawal.

Special Risk Patients:

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

Hepatic Impairment: 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. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Suicide: The risk of suicide is known to be increased in patients with substance abuse with or without concomitant depression. This risk is not abated by treatment with REVIA (see **ADVERSE REACTIONS**).

Information for Patients: It is recommended that the prescribing physician relate the following information to patients being treated with REVIA:

You have been prescribed REVIA as part of the comprehensive treatment for your alcoholism or drug dependence. You should carry identification to alert medical personnel to the fact that you are taking REVIA. A REVIA medication card may be obtained from your physician and can be used for this purpose. Carrying the identification card should help to ensure that you can obtain adequate treatment in an emergency. If you require medical treatment, be sure to tell the treating physician that you are receiving REVIA therapy.

Laboratory Tests: A high index of suspicion for drug-related hepatic injury is critical if the occurrence of liver damage induced by REVIA (naltrexone hydrochloride) is to be detected at the earliest possible time. Evaluations, using appropriate batteries of tests to detect liver injury are recommended at a frequency appropriate to the clinical situation and the dose of REVIA.

REVIA does not interfere with thin-layer, gas-liquid, and high pressure liquid chromatographic methods which may be used for the separation and detection of morphine, methadone or quinine in the urine. REVIA may or may not interfere with enzymatic methods for the detection of opioids depending on the specificity of the test. Please consult the test manufacturer for specific details.

Drug Interactions: Studies to evaluate possible interactions between REVIA and drugs other than opiates have not been performed. Consequently, caution is advised if the concomitant administration of REVIA and other drugs is required.

The safety and efficacy of concomitant use of REVIA and disulfiram is unknown, and the concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks.

Lethargy and somnolence have been reported following doses of REVIA and thioridazine.

Patients taking REVIA may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. In an emergency situation when opioid analgesia must be administered to a patient receiving REVIA, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged (see **PRECAUTIONS**).

Carcinogenesis, Mutagenesis and Impairment of Fertility: The following statements are based on the results of experiments in mice and rats. The potential carcinogenic, mutagenic and fertility effects of the metabolite 6-ß-naltrexol are unknown.

In a two-year carcinogenicity study in rats, 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 (600 mg/m^2/day; 16 times the recommended therapeutic dose, based on body surface area) 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 (600 mg/m^2/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.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the *Drosophila* recessive lethal assay, and in non-specific DNA repair tests with *E. coli*. However, no evidence of genotoxic potential was observed in a range of other *in vitro* tests, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an *in vivo* mouse micronucleus assay.

Naltrexone (100 mg/kg/day [600 mg/m^2/day] PO; 16 times the recommended therapeutic dose, based on body surface area) caused a significant increase in pseudopregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

Pregnancy: Category C. Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥ 30 mg/kg/day (180 mg/m^2/day; 5 times the recommended therapeutic dose, based on body surface area) and to rabbits at oral doses ≥ 60 mg/kg/day (720 mg/m^2/day; 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 200 mg/kg/day (32 and 65 times the recommended therapeutic dose, respectively, based on body surface area).

Rats do not form appreciable quantities of the major human metabolite, 6-ß-naltrexol; therefore, the potential reproductive toxicity of the metabolite in rats is not known.

There are no adequate and well-controlled studies in pregnant women. REVIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: Whether or not REVIA affects the duration of labor and delivery is unknown.

Nursing Mothers: In animal studies, naltrexone and 6-ß-naltrexol were excreted in the milk of lactating rats dosed orally with naltrexone. Whether or not REVIA is excreted in human milk is unknown. Because many drugs are excreted in human milk, caution should be exercised when REVIA is administered to a nursing woman.

Pediatric Use: The safe use of REVIA in pediatric patients younger than 18 years old has not been established.

ADVERSE REACTIONS:

During two randomized, double-blind placebo-controlled 12-week trials to evaluate the efficacy of REVIA as an adjunctive treatment of alcohol dependence, most patients tolerated REVIA well. In these studies, a total of 93 patients received REVIA at a dose of 50 mg once daily. Five of these patients discontinued REVIA because of nausea. No serious adverse events were reported during these two trials.

While extensive clinical studies evaluating the use of REVIA in detoxified, formerly opioid-dependent individuals failed to identify any single, serious untoward risk of REVIA use, placebo-controlled studies employing up to five-fold higher doses of REVIA (up to 300 mg per day) than that recommended for use in opiate receptor blockade have shown that REVIA causes hepatocellular injury in a substantial proportion of patients exposed at higher doses (see **WARNINGS** and **PRECAUTIONS: Laboratory Tests**).

Aside from this finding, and the risk of precipitated opioid withdrawal, available evidence does not incriminate REVIA, used at any dose, as a cause of any other serious adverse reaction for the patient who is "opioid-free." It is critical to recognize that REVIA can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

Patients with addictive disorders, especially opioid addiction, are at risk for multiple numerous adverse events and abnormal laboratory findings, including liver function abnormalities. Data from both controlled and observational studies suggest that these abnormalities, other than the dose-related hepatotoxicity described above, are not related to the use of REVIA.

Among opioid-free individuals, REVIA administration at therapeutic doses has not been associated with a predictable profile of serious adverse or untoward events. However, as mentioned above, among individuals using opioids, REVIA may cause serious withdrawal reactions (see **CONTRAINDICATIONS, WARNINGS, DOSAGE AND ADMINISTRATION**).

Reported Adverse Events:

REVIA has not been shown to cause significant increases in complaints in placebo-controlled trials in patients known to be free of opioids for more than 7-10 days. Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. This may represent the unmasking of occult opioid use, or it may represent symptoms attributable to naltrexone. A number of alternative dosing patterns have been recommended to try to reduce the frequency of these complaints (see **Individualization of Dosage**).

Alcoholism:

In an open label safety study with approximately 570 individuals with alcoholism receiving REVIA, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%).

Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing naltrexone, placebo, or controls undergoing treatment for alcoholism.

RATE RANGES OF NEW ONSET EVENTS

	Naltrexone	Placebo
Depression	0-15%	0-17%
Suicide Attempt/Ideation	0-1%	0-3%

Although no causal relationship with REVIA is suspected, physicians should be aware that treatment with REVIA does not reduce the risk of suicide in these patients (see **PRECAUTIONS**).

Opioid Addiction:

The following adverse reactions have been reported both at baseline and during the REVIA clinical trials in opioid addiction at an incidence rate of more than 10%:

Difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.

The incidence was less than 10% for:

Loss of appetite, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills.

The following events occurred in less than 1% of subjects:

Respiratory: nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath.
Cardiovascular: nose bleeds, phlebitis, edema, increased blood pressure, non-specific ECG changes, palpitations, tachycardia.
Gastrointestinal: excessive gas, hemorrhoids, diarrhea, ulcer.
Musculoskeletal: painful shoulders, legs or knees; tremors, twitching.
Genitourinary: increased frequency of, or discomfort during, urination; increased or decreased sexual interest.
Dermatologic: oily skin, pruritus, acne, athlete's foot, cold sores, alopecia.
Psychiatric: depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams.
Special senses: eyes–blurred, burning, light sensitive, swollen, aching, strained; ears–"clogged," aching, tinnitus.
General: increased appetite, weight loss, weight gain, yawning, somnolence, fever, dry mouth, head "pounding," inguinal pain, swollen glands, "side" pains, cold feet, "hot spells."
Post-marketing Experience: Data collected from post-marketing use of REVIA show that most events usually occur early in the course of drug therapy and are transient. It is not always possible to distinguish these occurrences from those signs and symptoms that may result from a

Depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with REVIA (naltrexone hydrochloride) used in the treatment of opioid dependence. No causal relationship has been demonstrated. In the literature, endogenous opioids have been theorized to contribute to a variety of conditions. In some individuals the use of opioid antagonists has been associated with a change in baseline levels of some hypothalamic, pituitary, adrenal, or gonadal hormones. The clinical significance of such changes is not fully understood.

Adverse events, including withdrawal symptoms and death, have been reported with the use of REVIA in ultra rapid opiate detoxification programs. The cause of death in these cases is not known (see **WARNINGS**).

Laboratory Tests: With the exception of liver test abnormalities (see **WARNINGS** and **PRECAUTIONS**), results of laboratory tests, like adverse reaction reports, have not shown consistent patterns of abnormalities that can be attributed to treatment with REVIA.

Idiopathic thrombocytopenic purpura was reported in one patient who may have been sensitized to REVIA in a previous course of treatment with REVIA. The condition cleared without sequelae after discontinuation of REVIA and corticosteroid treatment.

DRUG ABUSE AND DEPENDENCE:

REVIA is a pure opioid antagonist. It does not lead to physical or psychological dependence. Tolerance to the opioid antagonist effect is not known to occur.

OVERDOSAGE:

There is limited clinical experience with REVIA overdosage in humans. In one study, subjects who received 800 mg daily REVIA for up to one week showed no evidence of toxicity.

In the mouse, rat and guinea pig, the oral LD50s were 1,100-1,550 mg/kg; 1,450 mg/kg; and 1,490 mg/kg; respectively. High doses of REVIA (generally ≥1,000 mg/kg) produced salivation, depression/reduced activity, tremors, and convulsions. Mortalities in animals due to high-dose REVIA administration usually were due to clonic-tonic convulsions and/or respiratory failure.

Treatment of Overdosage: In view of the lack of actual experience in the treatment of REVIA overdose, patients should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date information.

DOSAGE AND ADMINISTRATION:

IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST AND DO NOT INITIATE REVIA THERAPY UNTIL THE NALOXONE CHALLENGE IS NEGATIVE.

Treatment of Alcoholism:

A dose of 50 mg once daily is recommended for most patients (see **Individualization of Dosage**). The placebo-controlled studies that demonstrated the efficacy of REVIA as an adjunctive treatment of alcoholism used a dose regimen of REVIA 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not evaluated in these trials.

A patient is a candidate for treatment with REVIA if:

- the patient is willing to take a medicine to help with alcohol dependence
- the patient is opioid-free for 7-10 days
- the patient does not have severe or active liver or kidney problems (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal.)
- the patient is not allergic to REVIA, and no other contraindications are present

Refer to **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** Sections for additional information.

REVIA should be considered as only one of many factors determining the success of treatment of alcoholism. Factors associated with a good outcome in the clinical trials with REVIA were the type, intensity, and duration of treatment; appropriate management of comorbid conditions; use of community-based support groups; and good medication compliance. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, especially medication compliance.

Treatment of Opioid Dependence:

Initiate treatment with REVIA using the following guidelines:

1. Treatment should not be attempted unless the patient has remained opioid-free for at least 7-10 days. Self-reporting of abstinence from opioids in opioid addicts should be verified by analysis of the patient's urine for absence of opioids. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms.
2. If there is any question of occult opioid dependence, perform a naloxone challenge test. If signs of opioid withdrawal are still observed following naloxone challenge, treatment with REVIA should not be attempted. The naloxone challenge can be repeated in 24 hours.
3. Treatment should be initiated carefully, with an initial dose of 25 mg of REVIA. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter.

Naloxone Challenge Test: The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The naloxone challenge test may be administered by either the intravenous or subcutaneous routes.

Intravenous:
Inject 0.2 mg naloxone.
Observe for 30 seconds for signs or symptoms of withdrawal.
If no evidence of withdrawal, inject 0.6 mg of naloxone.
Observe for an additional 20 minutes.

Subcutaneous:
Administer 0.8 mg naloxone.
Observe for 20 minutes for signs or symptoms of withdrawal.
Note: Individual patients, especially those with opioid dependence, may respond to lower doses of naloxone. In some cases, 0.1 mg IV naloxone has produced a diagnostic response.

Interpretation of the Challenge: Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include, but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, backache, bone or joint pains, tremors, sensations of skin crawling or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional naloxone should be administered.

Warning: If the test is positive, do NOT initiate REVIA therapy. Repeat the challenge in 24 hours. If the test is negative, REVIA therapy may be started if no other contraindications are present. If there is any doubt about the result of the test, hold REVIA and repeat the challenge in 24 hours.

Alternative Dosing Schedules:

Once the patient has been started on REVIA, 50 mg every 24 hours will produce adequate clinical blockade of the actions of parenterally administered opioids (i.e., this dose will block the effects of a 25 mg intravenous heroin challenge). A flexible approach to a dosing regimen may need to be employed in cases of supervised administration. Thus, patients may receive 50 mg of REVIA every weekday with a 100 mg dose on Saturday, 100 mg every other day, or 150 mg every third day. The degree of blockade produced by REVIA may be reduced by these extended dosing intervals.

There may be a higher risk of hepatocellular injury with single doses above 50 mg, and use of higher doses and extended dosing intervals should balance the possible risks against the probable benefits (see **WARNINGS** and **Individualization of Dosage**).

Patient Compliance:

REVIA should be considered as only one of many factors determining the success of treatment. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, including medication compliance.

HOW SUPPLIED:

REVIA (naltrexone hydrochloride) tablets are available in pale yellow 50 mg capsule-shaped film-coated tablets, scored and imprinted with "R11" on one side and "50" on the other, as follows:

Bottles of 30 Tablets	NDC 0056-0011-30
Bottles of 100 Tablets	NDC 0056-0011-70

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

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Appendix 2 Primary Toxicology Studies of Naltrexone and Bupropion

Drug	Study Type and Duration	Route of Administration	Species	Reference
Single-Dose Toxicity				
Naltrexone	Single-Dose LD_{50} (Mouse, Rat, Dog) or Acute Toxicity (Monkey)	PO, IV, SC PO, SC PO, SC PO	Mouse Rat Dog Monkey	Braude and Morrison (1976) Rosenkrantz (1984)
Bupropion	Single-Dose LD_{50}	PO, IP PO, IP	Mouse Rat	Tucker (1983)
Repeat-Dose Toxicity				
Naltrexone	90-Day 30-Day, 90-Day, 2-Year 90-Day 30-Day 1-Year	PO SC, PO PO SC PO	Mouse Rat Dog Dog Monkey	Rosenkrantz (1984) Braude and Morrison (1976)
Bupropion	12-week, 26-week, 55-week	PO	Rat	Tucker (1983)
	12-week, 52-week	PO	Dog	
Genotoxicity				
Naltrexone	Recessive Lethal Assay Reverse Mutation Assay DNA Damage *In Vivo* Micronucleus Test	Not Specified *In Vitro* *In Vitro* Not Specified	*Drosophila* - - Mouse	ReVia® Product Labeling Brusick et al. (1978)
Bupropion	Reverse Mutation Assay *In Vivo* Micronucleus Test	*In Vitro* PO	- Rat	Tucker (1983) Wellbutrin SR® Product Labeling
Carcinogenicity				
Naltrexone	2-Year	In-Feed	Mouse, Rat	Rosenkrantz (1984) ReVia® Product Labeling
Bupropion	96-Week 2-Year	PO	Mouse Rat	Tucker (1983)
Reproductive and Developmental Toxicity				
Naltrexone	Fertility and Reproduction Embryo-fetal Development Perinatal Development	PO	Rat Rat, Rabbit Rat	Christian (1984) ReVia® Product Labeling
Bupropion	Fertility and Development Embryo-fetal Development	PO	Rat Rat, Rabbit	Tucker (1983) Wellbutrin SR® Product Labeling

Appendix 3 Table of Clinical Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
BA	NB-233	Effect of Glyburide or food on the PK of Nal-SR and Bup-SR	Open-label, Single-Dose, Cross-Over	Nal-SR 8 mg/Bup-SR 90 mg trilayer tablet 1. Nal-SR 16 mg/ Bup-SR 180 mg, Single-dose, Fasted 2. Nal-SR 16 mg/ Bup-SR 180 mg + micronized glyburide, 6 mg, Single-dose, Fasted 3. Nal 16 mg/ Bup-SR 180 mg Single dose, Fed Oral	18	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 14-day washout period between treatments
Comparative BA/BE	NB-221	PK Study of Naltrexone Immediate and Sustained Release	Randomized, Single-Dose, Double-Blind, Cross-Over	Nal-SR 20 mg (4 x 5 mg Mini Tablets) Capsule Nal-IR 36 mg (3 x 12 mg Mini Tablets) Capsule 1. Nal-SR 40 mg, Single-dose, Fed 2 hrs before dosing 2. Nal-IR 36 mg, Single-dose, Fed 2 hrs before dosing Oral	40	Healthy Obese (30-45 kg/m^2)	1 Day Minimum 5-day washout period between treatments

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Comparative BA/BE	NB-225	PK study of Bup-SR in combination with Nal-IR or Nal-SR	Randomized, Double-Blind	Nal-SR 12.5 mg/Bup-SR 90 mg Capsule (Capsules contained 2.5 x 5 mg Nal-SR tablets and 1 90 mg Bup-SR tablet) Nal-IR 12 mg/ Bup-SR 90 mg Capsule (Capsules contained 1 x 12 mg Nal-IR tablet and 1 x 90 mg Bup-SR tablet) Maintenance Dose: 1. Nal-SR 25 mg/ Bup-SR 180 mg QAM; Nal-SR 12.5 mg/ Bup-SR 90 mg QPM (Total Daily Dose Nal-SR 37.5 mg/ Bup-SR 270 mg) 2. Nal-IR 24 mg/Bup-SR 180 mg QAM; Nal-IR 12 mg/ Bup-SR 90 mg QPM (Total Daily Dose Nal-IR 36 mg/ Bup-SR 270 mg) Oral	59	Healthy Obese (27-40 kg/m^2)	14 Days 7-day Titration Period

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Comparative BA/BE	NB-228	Relative BA study of intended commercial drug product manufactured at different sites	Randomized Single-Dose, Open-Label, Cross-Over	Nal-SR 8 mg/ Bup-SR 90 mg Trilayer Tablet (Patheon) Nal-SR 8 mg/ Bup-SR 90 mg Trilayer Tablet (PMRS/PharmOps) 1. Nal-SR 16 mg/Bup-SR 180 mg (Patheon), Single-dose, Fasted 2. Nal-SR 16 mg/Bup-SR 180 mg (PMRS- PharmOps), Single-dose, Fasted Oral	40	Healthy Patients (18-30 kg/m^2)	1 Day Minimum 9-day washout period between treatments
Comparative BA/BE	NB-229	Relative BA study of Nal-SR/ Bup-SR tablets manufactured at different sites	Randomized, Single-Dose, Open-Label, Cross-Over	Nal-SR 8 mg/Bup-SR 90 mg Trilayer Tablet (Patheon) Nal-SR 8 mg/Bup-SR 90 mg Trilayer Tablet (University of Iowa [UoI]) 1. Nal-SR16 mg/Bup-SR 180 mg (Patheon), Single-dose, Fasted 2. Nal-SR 16 mg/Bup-SR 180 mg (UoI), Single-dose, Fasted Oral	40	Healthy Patients (18-40 kg/m^2)	1 Day Minimum 14-day washout period between treatments

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Comparative BA/BE	NB-230	Relative BA of intended commercial drug product to commercially available tablet formulations of Nal-IR and Bup-SR	Randomized, Single-Dose, Open-Label, Cross-Over	Nal-SR 8 mg/ Bup-SR 90 mg Trilayer Tablet Nal-IR 50 mg Tablet Bup-SR 150 mg Tablet 1. Nal-SR 16 mg/ Bup-SR 180 mg, Single-dose, Fasted 2. Nal-IR 50 mg, Single-dose, Fasted 3. Bup-SR 150 mg, Single-dose, Fasted Oral	27	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 14-day washout period between treatments

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Comparative BA/BE	NB-231	Relative BA of 3 Nal-SR/ Bup-SR combination monolayer tablet formulations to the intended commercial drug product	Randomized, Single-Dose, Open-Label, Cross-Over, Pilot Study	Nal-SR 8 mg/ Bup-SR 90 mg Monolayer Tablet (Test 1) Nal-SR 8 mg/ Bup-SR 90 mg Monolayer Tablet (Test 2) Nal-SR 8 mg/ Bup-SR 90 mg Monolayer Tablet (Test 3) Nal-SR 8 mg/ Bup-SR 90 mg Trilayer Tablet 1. Nal-SR 16 mg/Bup-SR 180 mg (Test 1), Single-dose, Fasted 2. Nal-SR 16 mg/Bup-SR 180 mg (Test 2), Single-dose, Fasted 3. Nal-SR 16 mg/Bup-SR 180 mg (Test 3), Single-dose, Fasted 4. Nal-SR 16 mg/Bup-SR 180 mg (Trilayer) Single-dose, Fasted Oral	20	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 7-day washout period between treatments

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Comparative BA/BE	NB-237	Relative BA of 3 Nal-SR/ Bup-SR combination monolayer tablet formulations to the intended commercial drug product	Randomized, Single-Dose, Open-Label, Cross-Over, Pilot Study	Nal-SR 8 mg/ Bup-SR 90mg Monolayer Tablet (Test 1) Nal-SR 8 mg/ Bup-SR 90mg Monolayer Tablet (Test 2) Nal-SR 8 mg/ Bup-SR 90mg Monolayer Tablet (Test 3) Nal-SR 8 mg/ Bup-SR 90mg Trilayer Tablet 1. Nal-SR 16 mg/Bup-SR 180 mg (Test 1), Single-dose, Fasted 2. Nal-SR 16 mg/Bup-SR 180 mg (Test 2), Single-dose, Fasted 3. Nal-SR 16 mg/Bup-SR 180 mg (Test 3), Single-dose, Fasted 4. Nal-SR 16 mg/Bup-SR 180 mg (Trilayer), Single-dose, Fasted Oral	20	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 7-day washout period between treatments

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Comparative BA/BE	NB-238	Relative BA of 2 Nal-SR/ Bup-SR combination monolayer tablet formulations to the intended commercial drug product	Randomized, Single-Dose, Open-Label, Cross-Over, Pilot Study	Nal-SR 8 mg/ Bup-SR 90 mg Monolayer Tablet (Test 1) Nal-SR 8 mg/ Bup-SR 90 mg Monolayer Tablet (Test 2) Nal-SR 8 mg/ Bup-SR 90 mg Trilayer Tablet 1. Nal-SR 16 mg/Bup-SR 180 mg (Test 1), Single-dose, Fasted 2. Nal-SR 16 mg/Bup-SR 180 mg (Test 2), Single-dose, Fasted 3. Nal-SR 16 mg/Bup-SR 180 mg (Trilayer), Single-dose, Fasted Oral	18	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 7-day washout period between treatments
Comparative BA/BE	NB-239	Relative BA of a combination monolayer tablet to the intended commercial drug product	Randomized, Single-Dose, Open-Label, Cross-Over, Pilot Study	Nal-SR 8 mg/ Bup-SR 90 mg Monolayer Tablet Nal-SR 8 mg/ Bup-SR 90 mg Trilayer Tablet 1. Nal-SR 16 mg/Bup-SR 180 mg (Monolayer), Single-dose, Fed 2. Nal-SR 16 mg/Bup-SR 180 mg (Trilayer), Single-dose, Fed Oral	18	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 7-day washout period between treatments

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Descriptive Summary	AA88068	Compile descriptive statistics for the PK parameters of Nal-SR, Bup-SR and their metabolites following administration of the intended commercial drug product	n/a	n/a	206 included in the summary	n/a	n/a
Extrinsic Factor PK	NB-232	Effects of atorvastatin or valsartan on the PK of the intended commercial drug product, and relative BA of 2 commercial product presentations	Randomized, Single-Dose, Open-Label, Cross-Over	Nal-SR 8 mg/Bup-SR 90 mg Trilayer Tablet Nal-SR 4 mg/Bup-SR 90 mg Trilayer Tablet 1. Nal-SR, 16 mg/Bup-SR 180 mg, Single-dose, Fasted 2. Nal-SR 16 mg/Bup-SR 180 mg + atorvastatin, 80 mg tablet, Single-dose, Fasted 3. Nal-SR 16 mg/ Bup-SR 180 mg + valsartan 320 mg tablet, Single-dose, Fasted 4. Nal-SR, 8 mg/Bup-SR 180 mg, Single-dose, Fasted Oral	20	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 14-day washout period between treatments

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Extrinsic Factor PK	NB-234	Effect of nifedipine or lisinopril on the PK of naltrexone and bupropion	Randomized, Single-Dose, Open-Label, Cross-Over	Nal-SR 8 mg/Bup-SR 90 mg Trilayer Tablet 1. Nal-SR, 16 mg/Bup-SR 180 mg, Single-dose, Fasted 2. Nal-SR, 16 mg/Bup-SR 180 mg + nifedipine ER 90 mg tablet, Single-dose, Fasted 3. Nal-SR, 16 mg/ Bup-SR 180 mg + lisinopril IR 40 mg tablet, Single-dose, Fasted Oral	18	Healthy Patients (19-40 kg/m^2)	1 Day Minimum 14-day washout period between treatments
Extrinsic Factor PK	NB-236	Effect of the intended commercial drug product on the single-dose plasma PK of metoprolol, Steady State	Open-Label Cross-Over in Extension Period	Nal-SR, 8 mg/Bup-SR 90 mg Trilayer Tablet 1. Metoprolol, 50 mg IR tablet, Single-dose, Fed (Day 1) 2. Nal-SR 16 mg/ Bup-SR 90 mg BID, Fed (Maintenance Dose) 3. Nal-SR 16 mg/ Bup-SR 90 mg BID, + metoprolol 50 mg IR, Single-dose, Fed (Day 31) 4. Nal-SR 16 mg/ Bup-SR 90 mg BID, Fasted or Fed (Extension Period, Days 32-34) Oral	18	Healthy Patients (19-40 kg/m^2)	Up to 34 Days 21-Day Titration Period 3-Day Treatment Extension Period

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Graphical Analysis	COG 202390	Explore the relationships between naltrexone and bupropion exposure and the following: percent change from baseline weight; achievement of 5% responder status; and the occurrence of nausea	n/a	n/a	594 (input PK dataset) 849 (input PD dataset)	n/a	n/a
Population PK	Metrum 1	Population PK	Population PK	n/a	594	n/a	n/a
PD & PK Reports	IR-PET	Positron Emission Tomography (PET) study to characterize brain receptor occupancy of naltrexone	Open-Label	Nal-IR tablets compounded into capsules (Nal-IR) 1. Nal-IR 8 mg BID 2. Nal-IR 16 mg BID 3. Nal-IR 24 mg BID Oral	9	Healthy Overweight or Obese (>25 kg/m^2)	7 Days

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
PD & PK Reports	NB-222	PET study to characterize brain receptor occupancy of naltrexone SR	Open-Label	Nal-SR 10 mg (2 x 5 mg minitabs) Nal-SR 25 mg (5 x 5 mg minitabs) 1. Nal-SR 10 mg BID 2. Nal-SR 25 mg BID Oral	7	Healthy Obese (30-43 kg/m^2)	7 Days
PD Report	Metrum 2	Population PD	Population PD	n/a	849	n/a	n/a
Safety and Efficacy	OT-101	POC, Efficacy and Safety-Evaluate two different combination treatments	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 + PBO 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 Oral	358	Uncomplicated Obesity; Non-smoker (30-40 kg/m^2)	Up to 48 weeks Primary Treatment period 16 weeks Extension/ Crossover Period 32 weeks

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Efficacy and Safety	NB-201	Dose Finding; Efficacy and Safety	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 tablets 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 4. PBO + Nal-SR 24 mg/ BID 5. PBO + PBO/ BID 6. Bup-SR 200 mg + Nal-SR 16 mg/ BID Oral	419	Uncomplicated Obesity; Non-smoker (30-40 kg/m^2)	Up to 48 weeks Primary Treatment 24 weeks Extension/ Crossover Period 24 weeks
Safety	NB-201 Sub-study	Evaluate change in visceral and total fat	Randomized, Double-Blind, PBO-Controlled	Same as Parent Study NB-201 (above)	107	Eligible Patients from the Parent NB-201 Study	24 weeks

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Efficacy and Safety	NB-301	Long term Efficacy and Safety with a discontinuation period	Randomized, Double-Blind, PBO-Controlled	Nal-SR 4 mg / Bup-SR 90 mg (4/90) Tablet Nal-SR 8 mg / Bup-SR 90 mg (8/90) Tablet Maintenance dose: 1. Nal-SR 4 mg/ Bup-SR 180 mg/ BID 2. Nal-SR 8 mg/ Bup-SR 180 mg/ BID 3. Placebo/ BID Oral	1742	Uncomplicated Obesity or Overweight Associated with Controlled Hypertension and/or Dyslipidemia (27-45 kg/m^2)	57 weeks Titration Period 4 weeks Drug Maintenance Period 52 weeks Discontinuation Period 2 weeks (dosing during Wk 57 but not Wk 58)
Safety	NB-301 Sub-study	Evaluate change in visceral and total fat	Randomized, Double-Blind, PBO-Controlled	Same as Parent Study NB-301 (above)	214	Eligible Patients from the Parent NB-301 Study	Up to 56 weeks (Last eval within 14 days of completion of the Wk 52 Parent study visit)
Efficacy and Safety	NB-302	Long-Term Efficacy and Safety in patients participating in a behavior modification program	Randomized, Double-Blind, PBO-Controlled	Nal-SR 8 mg/ Bup-SR 90 mg (8/90) Tablet Maintenance dose: 1.Nal-SR 16 mg/Bup-SR 180 mg/ BID 2.Placebo BID Oral	793	Uncomplicated Obesity or Overweight Associated with Controlled Hypertension and/or Dyslipidemia: Non-smoker (27-45 kg/m^2)	56 weeks Titration Period 4 weeks Drug Maintenance Period 52 weeks

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Efficacy and Safety	NB-303	Long-Term Efficacy and Safety with two alternative titration periods and re-randomization for non-responders	Randomized, Double-Blind, PBO-Controlled,	Nal-SR 4 mg / Bup-SR 90 mg (4/90) Tablet Nal-SR 8 mg / Bup-SR 90 mg (8/90) Tablet Nal-SR 12 mg/Bup-SR 90 mg (12/90) Tablet Maintenance dose: 1. Nal-SR 16 mg/ Bup-SR 180 mg BID 2. Placebo BID Re-randomization dose: 3. Nal-SR 24 mg/ Bup-SR 180 mg BID Oral	1496	Uncomplicated Obesity or Overweight Associated with Controlled Hypertension and/or Dyslipidemia (27-45 kg/m^2)	56 weeks Titration Period (Fast 4 weeks or Slow 5 weeks) Drug Maintenance Period 52 weeks Beginning Wk 28-44 Re-Randomization for non-responders
Safety	NB-303 Sub-study	Ambulatory Blood Pressure Monitoring	Randomized, Double-Blind, PBO-Controlled	Same as Parent Study NB-303 (above)	182	Eligible Patients from the Parent NB-303 Study	Up to 56 weeks (Last eval 14 days of completion of the Wk 52 Parent study visit)

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
Efficacy and Safety	NB-304	Long-Term Efficacy and Safety in patients with type II diabetes	Randomized, Double-Blind, PBO-Controlled	Nal-SR 8 mg /Bup-SR 90 mg (8/90) Tablet Maintenance dose: 1. Nal-SR 16 mg/ Bup-SR 180 mg BID 2. Placebo Oral	505	Overweight and Obese Patients with Type 2 Diabetes (27-45 kg/m^2)	56 weeks Titration Period 4 weeks Drug Maintenance Period 52 weeks
Efficacy and Safety Un-controlled	NB-401	Evaluate Efficacy and Safety in overweight or obese nicotine-dependent patients	Exploratory, Open-Label	Nal-SR 8 mg / Bup-SR 90 mg (8/90) Tablet Maintenance dose: 1. Nal-SR 16 mg/Bup-SR 180 mg BID Oral	30	Overweight or Obese Patients who are Nicotine-Dependent (27-45 kg/m^2)	24 weeks Titration Period 4 weeks Drug Maintenance Period 20 weeks
Efficacy and Safety Un-controlled	NB-402	Evaluate Efficacy and Safety in overweight or obese patients with major depression	Exploratory, Open-Label	Nal-SR 8 mg /Bup-SR 90 mg (8/90) Tablet Maintenance dose: 1. Nal-SR 16 mg/Bup-SR 180 mg BID Oral	25	Overweight or Obese Patients with Major Depression (27-43 kg/m^2)	24 weeks Titration Period 4 weeks Drug Maintenance Period 20 weeks

Appendix 3 Table of Clinical Studies (*Continued*)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Patients Enrolled	Healthy Patients or Diagnosis of Patients (BMI)[a]	Duration of Treatment
fMRI	NB-431	Evaluate Functional Magnetic Resonance Imaging (fMRI) changes in obese patients taking Nal-SR/ Bup-SR	Randomized, Double-Blind, PBO-Controlled	Nal-SR 8 mg/ Bup-SR 90 mg tablets Maximum dose: 1. Nal-SR 16 mg/Bup-SR 180 mg BID 2. Placebo BID Oral	40 Planned 29 patients enrolled as of 15 SEP 2009	Healthy Overweight or Obese Females (27-40 kg/m^2)	4 Weeks Titration Period 4 weeks (maximum dosing during week 4)

Definitions: BID = twice daily; Bup-SR = bupropion sustained-release; Flu = fluoxetine; fMRI=functional magnetic resonance imaging; Nal-IR = naltrexone immediate release; Nal-SR = naltrexone sustained release; PBO = placebo; PET = positron emission tomography; PD=pharmacodynamics: PK=pharmacokinetics; POC = proof of concept; SR = sustained release.

a = Body Mass Index (BMI) listed are inclusion criteria for each study.

Appendix 4 Potential Drug-Drug Interactions

Table 54 Potential Drug-Drug Interactions: Effects of NB on Other Drugs

Naltrexone	**Bupropion**
Effect on Drugs Metabolized by CYP2D6	
None Expected	Metoprolol: AUC & C_{max} ↑4-fold and 2-fold Desipramine: AUC & C_{max} ↑5-fold and 2-fold Venlafaxine: C_{trough} ↑~3-fold Paroxetine: No significant change in C_{trough} Fluoxetine: No significant change in C_{trough}
Effect on Cationic Drugs	
None Expected	In vitro study predicts potential interaction with OCT2 substrates (e.g., metformin, pindolol, ranitidine and varenicline) similar to the positive control, cimetidine. Clinical results indicate serum concentrations of creatinine (an endogenous OCT2 substrate) are increased approximately 8% by bupropion treatment and 22% with cimetidine. Based on relative clinical effects on creatinine secretion, interaction expected to be no worse than cimetidine which caused a 40% increase in AUC and 60% increase in C_{max} of metformin.
Other	
Acamprosate: AUC & C_{max} ↑ 25% & 33% No interaction observed between naltrexone and atorvastatin, lisinopril, valsartan, diazepam (and its nordiazepam metabolite)	No interaction observed between bupropion and atorvastatin, lisinopril, valsartan, lopinavir/ritonavir, lamotrigine, or varenicline.

Table 55 Potential Drug-Drug Interactions: Effects of Other Drugs on NB

Naltrexone (N) and 6β naltrexol (6β)			Bupropion (B), Hydroxybupropion (HB), Threohydrobupropion (TB), and Erythrohydrobupropion (EB)		
Effects of Drugs that Induce CYP on NB					
None Expected			Carbamazepine	B	AUC & C_{max} ↓ 90% & 87%
				HB	AUC & C_{max} ↑ 50% & 71%
				TB	AUC & C_{max} ↓ 86% & 81%
				EB	AUC & C_{max} ↓ 96% & 86%
			Efavirenz	B	AUC & C_{max} ↓ 55% & 34%
				HB	C_{max} ↑ 50%
			Lopinavir/ Ritonavir	B	AUC & C_{max} ↓ 57% & 57%
				HB	AUC & C_{max} ↓ 50% & 31%
			Rifampin	B	AUC & C_{max} ↓ 50% & 35%
				HB	AUC & C_{max} ↓ 36% & ↑ 49%
Effects of Drugs that Inhibit CYP2B6 on NB					
None Expected			Prasugrel	B	AUC & C_{max} ↑ 18% & 14%
				HB	AUC & C_{max} ↓ 23% & 32%
			Clopidogrel	B	AUC & C_{max} ↑ 60% & 40%
				HB	AUC & C_{max} ↓ 52% & 50%
			Ticlopidine	B	AUC & C_{max} ↑ 85% & 38%
				HB	AUC & C_{max} ↓ 84% & 78%
			HRT	B	C_{max} ↑ 21%
				HB	AUC & C_{max} ↓ 47% & 56%
Other					
Nifedipine*	N	AUC & C_{max} ↑24% & 58%	OC	B	AUC ↓ 19%
	6β	No effect		HB	AUC & C_{max} ↓ 31% & 20%
Glyburide*	N	AUC & C_{max} ↑1.9- & 2.1-fold	Valproate	B	No significant change in AUC or C_{max}
	6β	No effect		HB	AUC & C_{max} ↑ 94% & 56%
Metoprolol	N	AUC & C_{max} ↓ 25% & 29%	Cimetidine	B	No Effect
	6β	No effect		HB	No Effect
*Attributed to food effect of naltrexone. Nifedipine alters gastric transit time and glyburide is co-administered with an oral glucose solution of over 1000 calories.				TB/EB	AUC & C_{max} ↑ 16% & 32%
			Nifedipine*	B	C_{max} ↑ 22%
			Glyburide*	B	AUC & C_{max} ↑ 36% & 18%
				HB	AUC & C_{max} ↑ 23% & 15%
			* Attributed to food effect on single dose bupropion. Nifedipine alters gastric transit time and glyburide is co-administered with an oral glucose solution of over 1000 calories		
No effect of atorvastatin, lisinopril, or valsartan on PK of naltrexone or its metabolite.			No effect of atorvastatin, lisinopril, metoprolol, or valsartan on PK of bupropion or its metabolites.		

No effect denotes the 90% CI is within 80-125%.

HRT= Hormone replacement therapy (estradiol valerate + levonorgestrel)

OC= Oral contraceptive (ethinyl estradiol + desogestrel)

Appendix 5 Closed Testing Procedure for Secondary Endpoints

Table 56 Sequential Order for Secondary Efficacy Objectives (CTP)

SECONDARY EFFICACY MEASURES (CTP ORDER)	NB-301	NB-302	NB-303	NB-304
Percent change in body weight from baseline and the Week 56 visit (LOCF)	NA	NA	1	NA
Proportion of patients with ≥5% decrease in total body weight from baseline to endpoint (Week 56 LOCF)	NA	NA	2	NA
Change in HbA1c from baseline and the Week 56 visit (LOCF)	NA	NA	NA	1
Proportion of patients with a decrease in HbA1c below 7% at endpoint (Week 56 LOCF)	NA	NA	NA	7
Proportion of patients with ≥10% decrease in total body weight from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	1	1	3	6
Change in waist circumference from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	2	2	4	5
Change in fasting triglycerides from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	4	3	6	2
Change in fasting insulin from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	7	4	9	11
Change in fasting HDL from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	3	5	5	3
Change in IWQOL- Lite total score from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	5	6	7	13
Change in HOMA-IR from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	9	7	11	10
Change in hs-CRP from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	6	8	8	14
Change in fasting blood glucose from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	8	9	10	4
Change in fasting LDL from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	11	10	13	17
Change in systolic blood pressure from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	12	11	14	18
Change in diastolic blood pressure from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	13	12	15	19
Change in IDS-SR total score from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	14	13	16	20
Change in FCI sweets subscale scores from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	15	14	17	21
Change in FCI carbohydrates/starches subscale score from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	16	15	18	22
Change in COE Item 19 from baseline to endpoint (Week 56 LOCF; Week 28 for study NB-303)	10	NA	12	16
Proportion of patients with HbA1c <6.5% at endpoint (Week 56 LOCF)	NA	NA	NA	12
Percent of patients requiring changes in dose(s) of oral hypoglycemic medication	NA	NA	NA	9
Percent of patients requiring rescue medications for diabetes	NA	NA	NA	8

Table 56 Sequential Order for Secondary Efficacy Objectives (CTP) (*Continued*)

SECONDARY EFFICACY MEASURES (CTP ORDER)	NB-301	NB-302	NB-303	NB-304
Percent of patient discontinuing study drug due to poor glycemic control	NA	NA	NA	15

Abbreviations: COE = Control of Eating Questionnaire, CTP=closed testing procedure, FCI = Food Craving Inventory, HbA1C = hemoglobin A1C, HDL = High Density Lipoprotein, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, hs-CRP = High Sensitivity C-Reactive Protein, IDS-SR=Inventory of Depressive Symptomatology-Self Reported, IWQOL-Lite = Impact of Weight on Quality of Life Questionnaire-Lite Version, LOCF = Last Observation Carried Forward, NA = Not Applicable.

Table 57 Overview of Secondary Efficacy Variables by CTP: Study NB-301, Full Analysis Set

Secondary Efficacy Variables (Sequential Order)	NB16 p-value	NB32 p-value
Body Weight – Proportion of Patients with ≥10% Decrease from Baseline to Endpoint[a]	p<0.001*	p<0.001*
Change from Baseline to Endpoint:		
Waist circumference	p<0.001*	p<0.001*
Fasting HDL cholesterol levels	p<0.001*	p<0.001*
Fasting triglycerides levels[b]	p=0.046*	p<0.001*
IWQOL-Lite total scores	p<0.001*	p<0.001*
hs-CRP levels[b]	p=0.016*	p=0.008*
Fasting insulin levels[b]	p=0.063	p<0.001*
Fasting blood glucose levels	NA	p=0.010*
HOMA-IR levels[b]	NA	p<0.001*
21-item COE, item #19	NA	p<0.001*
Fasting LDL cholesterol levels	NA	p=0.484
Systolic blood pressure	NA	NA
Diastolic blood pressure	NA	NA
IDS-SR total score	NA	NA
FCI sweets subscale score	NA	NA
FCI carbohydrates subscale score	NA	NA

* p<0.05 (two-sided significance); all such noted results favor NB16 or NB32 over placebo.

a. p-value was calculated based on the odds ratio.

b. Least squares percent change was calculated for secondary efficacy variables analyzed using log10 transformed data.

Notes:

(1) Full analysis set included all patients who were randomized, had a baseline weight measurement, and had at least one postbaseline weight measurement while on study drug.

(2) 21-item COE questionnaire included 21 individual scores.

(3) p-values were calculated for LS means differences unless otherwise noted.

Abbreviations: COE = Control of Eating Questionnaire, CTP=closed testing procedure, FCI = Food Craving Inventory, HDL = High Density Lipoprotein, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, hs-CRP = High Sensitivity C-Reactive Protein, IDS-SR=Inventory of Depressive Symptomatology-Self Reported, IWQOL-Lite = Impact of Weight on Quality of Life Questionnaire-Lite Version, LDL=low density lipid protein; NA = Not Applicable (in accordance with the closed testing procedure, no further hypothesis testing was performed).

Table 58 Overview of Secondary Efficacy Variables by CTP: Study NB-302, Full Analysis Set

Secondary Efficacy Variables (Sequential Order)	NB32 p-value
Body Weight – Proportion of Patients with ≥10% Decrease from Baseline to Endpoint[a]	p<0.001*
Change from Baseline to Endpoint:	
Waist circumference	p<0.001*
Fasting triglycerides levels[b]	p=0.004*
Fasting insulin levels[b]	p=0.003*
Fasting HDL cholesterol levels	p<0.001*
IWQOL-Lite total scores	P=0.001*
HOMA-IR levels[b]	p=0.003*
hs-CRP levels[b]	p=0.165
Fasting blood glucose levels	NA
Fasting LDL cholesterol levels	NA
Systolic blood pressure	NA
Diastolic blood pressure	NA
IDS-SR total score	NA
FCI sweets subscale score	NA
FCI carbohydrates subscale score	NA
21-item COE, item #19	NA

* p<0.05 (two-sided significance); all such noted results favor NB32 over placebo.

a. p-value was calculated based on the odds ratio.

b. Least squares percent change was calculated for secondary efficacy variables analyzed using log10 transformed data.

Notes:

(1) Full analysis set included all patients who were randomized, had a baseline weight measurement, and had at least one postbaseline weight measurement while on study drug.

(2) p-values were calculated for LS means differences unless otherwise noted.

Abbreviations: COE = Control of Eating Questionnaire, CTP=closed testing procedure, FCI = Food Craving Inventory, HDL = High Density Lipoprotein, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, hs-CRP = High Sensitivity C-Reactive Protein, IDS-SR=Inventory of Depressive Symptomatology-Self Reported, IWQOL-Lite = Impact of Weight on Quality of Life Questionnaire-Lite Version, LDL=low density lipoprotein; NA = Not Applicable (in accordance with the closed testing procedure, no further hypothesis testing was performed).

Table 59 Overview of Secondary Efficacy Variables by CTP: Study NB-303, Full Analysis Set

Secondary Efficacy Variables (Sequential Order)	NB32 p-value
Body Weight – Percent change from Baseline to Week 56 (weighted LOCF)	p<0.001*
Body Weight – Proportion of Patients with ≥5% Decrease from Baseline to Week 56 (weighted LOCF)[a]	p<0.001*
Body Weight – Proportion of Patients with ≥10% Decrease from Baseline to Week 56 (weighted LOCF)[a]	p<0.001*
Change from Baseline to Week 28 (LOCF):	
Waist circumference	p<0.001*
Fasting HDL cholesterol levels	p<0.001*
Fasting triglycerides levels[b]	p=0.007*
IWQOL-Lite total scores	p<0.001*
hs-CRP levels[b]	p=0.091
Fasting insulin levels[b]	NA
Fasting blood glucose levels	NA
HOMA-IR levels[b]	NA
21-item COE, item #19	NA
Fasting LDL cholesterol levels	NA
Systolic blood pressure	NA
Diastolic blood pressure	NA
IDS-SR total score	NA
FCI sweets subscale score	NA
FCI carbohydrates subscale score	NA

* p<0.05 (two-sided significance); all such noted results favor NB32 over placebo.

a. p-value was calculated based on the odds ratio.

b. Least squares percent change was calculated for secondary efficacy variables analyzed using log10 transformed data.

Notes:

(1) Full analysis set included all patients who were randomized, had a baseline weight measurement, and had at least one postbaseline weight measurement while on study drug.

(2) p-values were calculated for LS means differences unless otherwise noted.

Abbreviations: COE = Control of Eating Questionnaire, CTP=closed testing procedure, FCI = Food Craving Inventory, HbA1C = hemoglobin A1C, HDL = High Density Lipoprotein, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, hs-CRP = High Sensitivity C-Reactive Protein, IDS-SR=Inventory of Depressive Symptomatology-Self Reported, IWQOL-Lite = Impact of Weight on Quality of Life Questionnaire-Lite Version, LDL = low density lipoprotein; NA = Not Applicable (in accordance with the closed testing procedure, no further hypothesis testing was performed).

Table 60 Overview of Secondary Efficacy Variables by CTP: Study NB-304, Full Analysis Set

Secondary Efficacy Variables (Sequential Order)	NB32 p-value
HbA1c Levels Change from Baseline to Endpoint	p<0.001*
Fasting Triglycerides Levels Change from Baseline to Endpoint[b]	p=0.007*
Fasting HDL Cholesterol Levels Change from Baseline to Endpoint	p<0.001*
Fasting Blood Glucose Levels Change from Baseline to Endpoint	p=0.065
Waist Circumference Change from Baseline to Endpoint	NA
Body Weight – Proportion of Patients with ≥10% Decrease from Baseline to Endpoint[a]	NA
HbA1c - Proportion of Patients with <7% at Endpoint[a]	NA
Requiring Rescue Medications for Diabetes - Percent of Patients[a]	NA
Requiring Change (Reduction [↓] and Increase [↑]) in Dose(s) of Oral Antidiabetes Medication - Percent of Patients[a]	NA
HOMA-IR Levels Change from Baseline to Endpoint[b]	NA
Fasting Insulin Levels Change from Baseline to Endpoint[b]	NA
HbA1c - Proportion of Patients with <6.5% at Endpoint[a]	NA
IWQOL-Lite Total Scores Change from Baseline to Endpoint	NA
hs-CRP Levels Change from Baseline to Endpoint[b]	NA
Discontinued Due to Poor Glycemic Control - Percent of Patients[a]	NA
COE Item #19 Scores Change from Baseline to Endpoint	NA
Fasting LDL Cholesterol Levels Change from Baseline to Endpoint	NA
Systolic Blood Pressure Change from Baseline to Endpoint	NA
Diastolic Blood Pressure Change from Baseline to Endpoint	NA
IDS-SR Total Scores Change from Baseline to Endpoint	NA
FCI Sweets and carbohydrates/starches Subscale Score Change from Baseline to Endpoint	NA

* p<0.05 (two-sided significance); all such noted results favor NB32 over placebo.

a. p-value was calculated based on the odds ratio.

b. Least squares percent change was calculated for secondary efficacy variables analyzed using log10 transformed data.

Notes:

(1) Full analysis set included all patients who were randomized, had a baseline weight measurement, and had at least one postbaseline weight measurement while on study drug.

(2) p-values were calculated for LS means differences unless otherwise noted.

Abbreviations: COE = Control of Eating Questionnaire, CTP=closed testing procedure, FCI = Food Craving Inventory, HDL = High Density Lipoprotein, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, hs-CRP = High Sensitivity C-Reactive Protein, IDS-SR=Inventory of Depressive Symptomatology-Self Reported, IWQOL-Lite = Impact of Weight on Quality of Life Questionnaire-Lite Version, ; LDL = low density lipoprotein; NA = Not Applicable (in accordance with the closed testing procedure, no further hypothesis testing was performed).

Appendix 6 Flow Charts of Patient Disposition for the Phase 3 Studies

Figure 40 Patient Disposition: Study NB-301

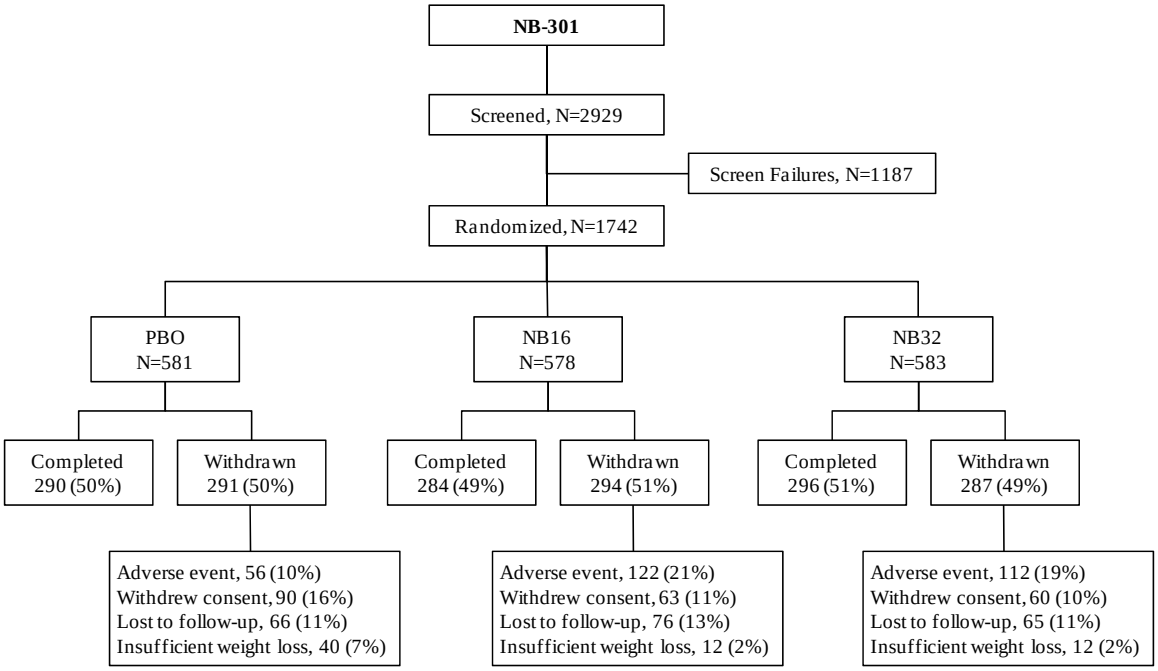


Figure 41 Patient Disposition: Study NB-302

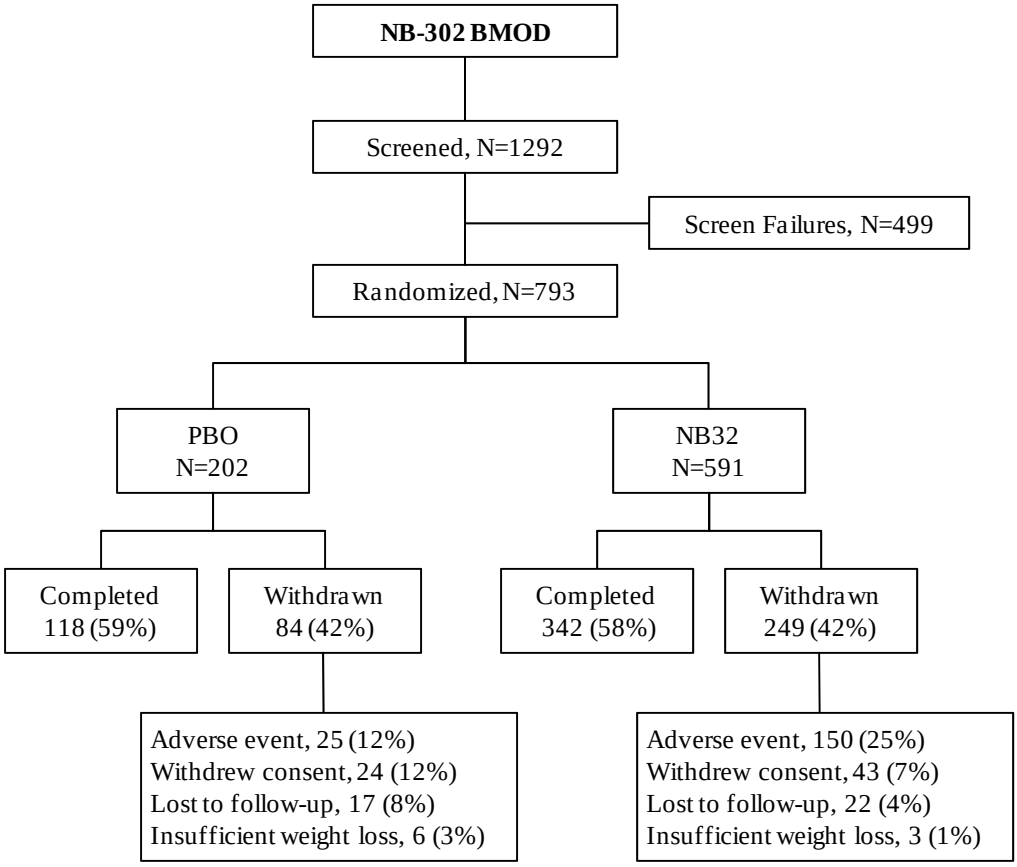


Figure 42 Patient Disposition: Study NB-303

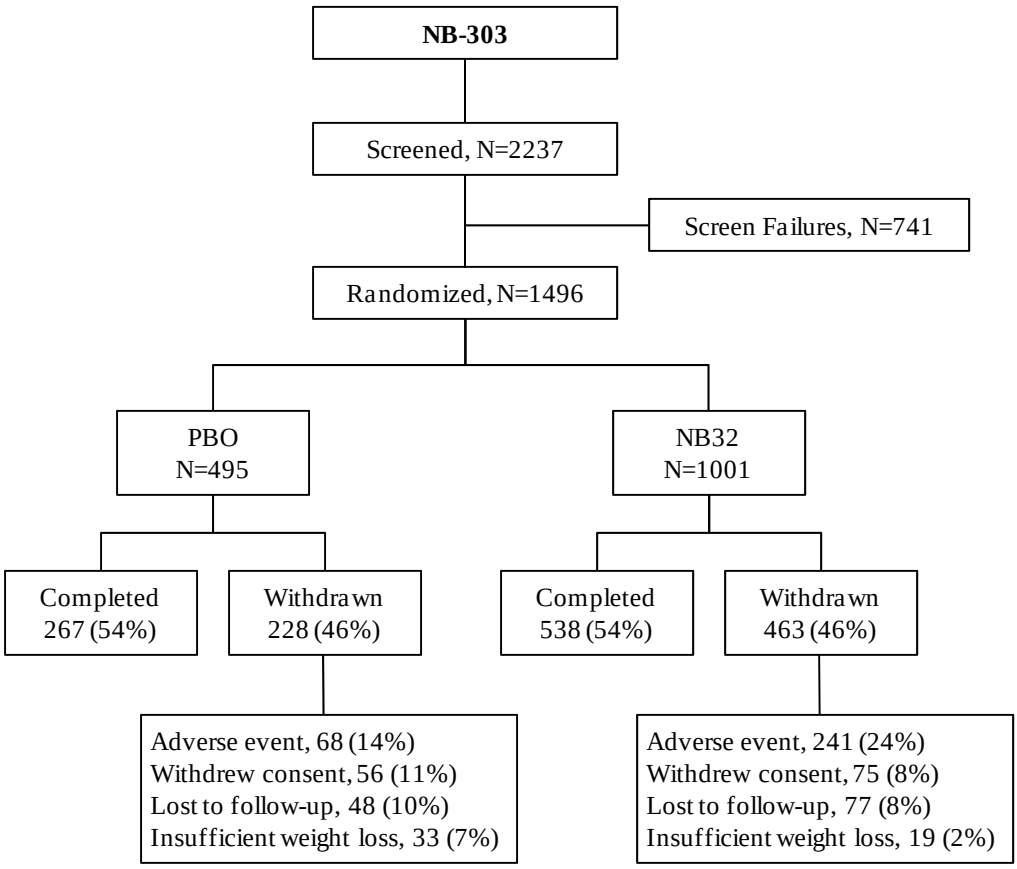
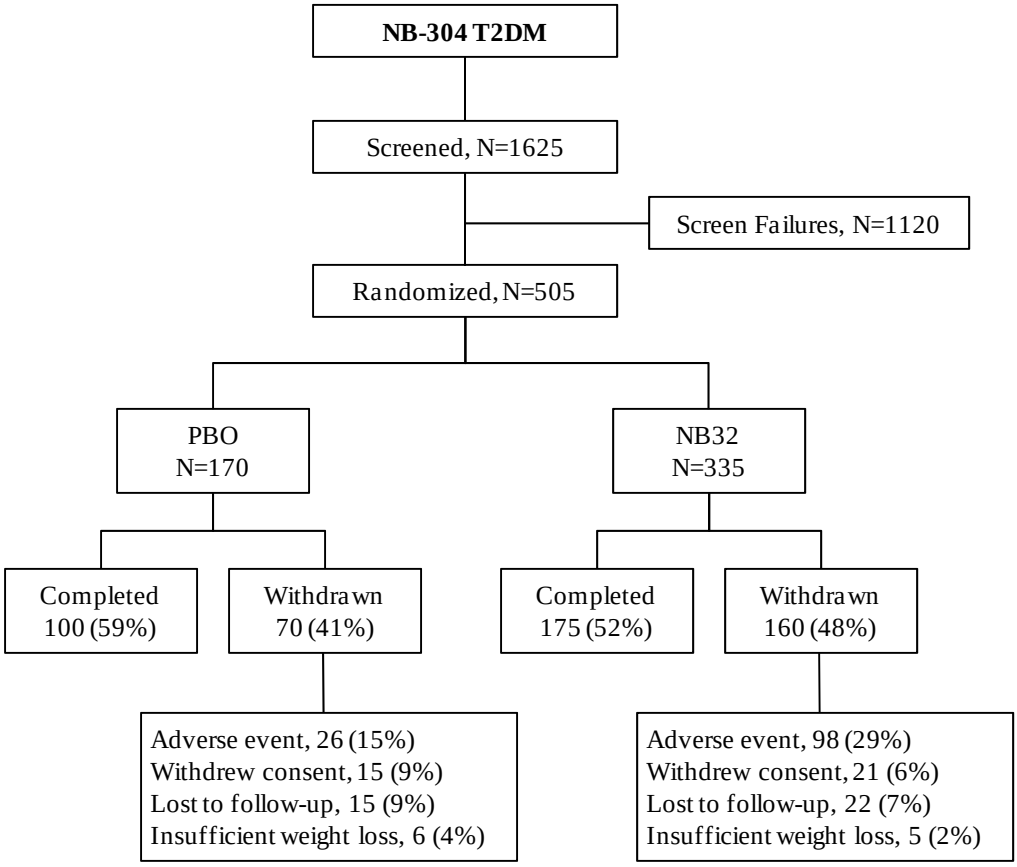


Figure 43 Patient Disposition: Study NB-304



Appendix 7 Preferred Terms by Subtopics, SMQ, or TME Grouping for Special Topics of Medical Interest

Table 61 Hypertension, Tachyarrhythmia, and Arrhythmia SMQs by Preferred Term

Hypertension SMQ	
Accelerated hypertension	Hypertensive cardiomegaly
Aldosterone urine abnormal	Hypertensive cardiomyopathy
Aldosterone urine increased	Hypertensive crisis
Angiotensin converting enzyme increased	Hypertensive emergency
Angiotensin I increased	Hypertensive encephalopathy
Angiotensin II increased	Hypertensive heart disease
Blood aldosterone abnormal	Hypertensive nephropathy
Blood aldosterone increased	Labile blood pressure
Blood catecholamines abnormal	Labile hypertension
Blood catecholamines increased	Malignant hypertension
Blood pressure abnormal	Malignant hypertensive heart disease
Blood pressure ambulatory abnormal	Malignant renal hypertension
Blood pressure ambulatory increased	Maternal hypertension affecting foetus
Blood pressure diastolic abnormal	Metabolic syndrome
Blood pressure diastolic increased	Metanephrine urine abnormal
Blood pressure fluctuation	Metanephrine urine increased
Blood pressure inadequately controlled	Neurogenic hypertension
Blood pressure increased	Non-dipping
Blood pressure management	Norepinephrine abnormal
Blood pressure orthostatic abnormal	Norepinephrine increased
Blood pressure orthostatic increased	Orthostatic hypertension
Blood pressure systolic abnormal	Pre-eclampsia
Blood pressure systolic increased	Pregnancy induced hypertension
Catecholamines urine abnormal	Prehypertension
Catecholamines urine increased	Primary hyperaldosteronism
Diastolic hypertension	Procedural hypertension
Diuretic therapy	Pseudoaldosteronism
Eclampsia	Renal hypertension
Ectopic aldosterone secretion	Renin abnormal
Ectopic renin secretion	Renin increased
Endocrine hypertension	Renin-angiotensin system inhibition
Essential hypertension	Renovascular hypertension
HELLP syndrome	Retinopathy hypertensive
Hyperaldosteronism	Secondary aldosteronism
Hypertension	Secondary hypertension
Hypertension neonatal	Tyramine reaction
Hypertensive angiopathy	Withdrawal hypertension

Table 61 Hypertension, Tachyarrhythmia, and Arrhythmia SMQs by Preferred Term (*Continued*)

Tachyarrhythmia SMQ	
Arrhythmia supraventricular	Tachyarrhythmia
Atrial fibrillation	Accelerated idioventricular rhythm
Atrial flutter	Cardiac fibrillation
Atrial tachycardia	Parasystole
ECG P wave inverted	Rhythm idioventricular
Electrocardiogram P wave abnormal	Torsade de pointes
Sinus tachycardia	Ventricular arrhythmia
Supraventricular extrasystoles	Ventricular extrasystoles
Supraventricular tachyarrhythmia	Ventricular fibrillation
Supraventricular tachycardia	Ventricular flutter
Anomalous atrioventricular excitation	Ventricular pre-excitation
Atrioventricular extrasystoles	Ventricular tachyarrhythmia
Cardiac flutter	Ventricular tachycardia
Extrasystoles	
Arrhythmia SMQ	
Accelerated idioventricular rhythm	Extrasystoles
Accessory cardiac pathway	Foetal arrhythmia
Adams-Stokes syndrome	Foetal heart rate deceleration
Agonal rhythm	Foetal heart rate disorder
Anomalous atrioventricular excitation	Gallop rhythm present
Arrhythmia	Heart alternation
Arrhythmia neonatal	Heart block congenital
Arrhythmia supraventricular	Heart rate abnormal
Arrhythmogenic right ventricular dysplasia	Heart rate decreased
Atrial conduction time prolongation	Heart rate increased
Atrial fibrillation	Heart rate irregular
Atrial flutter	Long QT syndrome
Atrial tachycardia	Long QT syndrome congenital
Atrioventricular block	Loss of consciousness
Atrioventricular block complete	Lown-Ganong-Levine syndrome
Atrioventricular block first degree	Neonatal tachycardia
Atrioventricular block second degree	Nodal arrhythmia
Atrioventricular conduction time shortened	Nodal rhythm
Atrioventricular extrasystoles	Pacemaker generated arrhythmia
AV dissociation	Palpitations
Bifascicular block	Parasystole
Bradyarrhythmia	Paroxysmal arrhythmia
Bradycardia	Rebound tachycardia
Bradycardia foetal	Reperfusion arrhythmia
Bradycardia neonatal	Rhythm idioventricular
Brugada syndrome	Sick sinus syndrome
Bundle branch block	Sinoatrial block
Bundle branch block bilateral	Sinus arrest
Bundle branch block left	Sinus arrhythmia
Bundle branch block right	Sinus bradycardia
Cardiac arrest	Sinus tachycardia
Cardiac arrest neonatal	Sudden cardiac death
Cardiac death	Sudden death
Cardiac fibrillation	Supraventricular extrasystoles
Cardiac flutter	Supraventricular tachyarrhythmia
Cardiac telemetry abnormal	Supraventricular tachycardia

Table 61 Hypertension, Tachyarrhythmia, and Arrhythmia SMQs by Preferred Term (*Continued*)

Arrhythmia SMQ (continued)	
Cardio-respiratory arrest	Syncope
Cardio-respiratory arrest neonatal	Tachyarrhythmia
Chronotropic incompetence	Tachycardia
Conduction disorder	Tachycardia foetal
ECG P wave inverted	Tachycardia paroxysmal
Electrocardiogram abnormal	Torsade de pointes
Electrocardiogram ambulatory abnormal	Trifascicular block
Electrocardiogram change	Ventricular arrhythmia
Electrocardiogram delta waves abnormal	Ventricular asystole
Electrocardiogram P wave abnormal	Ventricular extrasystoles
Electrocardiogram PQ interval prolonged	Ventricular fibrillation
Electrocardiogram PR prolongation	Ventricular flutter
Electrocardiogram PR shortened	Ventricular pre-excitation
Electrocardiogram QRS complex prolonged	Ventricular tachyarrhythmia
Electrocardiogram QT prolonged	Ventricular tachycardia
Electrocardiogram repolarisation abnormality	Wandering pacemaker
Electrocardiogram RR interval prolonged	Withdrawal arrhythmia
Electrocardiogram U-wave abnormality	Wolff-Parkinson-White syndrome
Electrocardiogram U-wave biphasic	Wolff-Parkinson-White syndrome congenital
Electromechanical dissociation	

Table 62 Ischemic Heart Disease SMQ by Preferred Term

Ischemic Heart Disease SMQ	
Acute coronary syndrome	Electrocardiogram Q wave abnormal
Acute myocardial infarction	Electrocardiogram ST segment abnormal
Angina pectoris	Electrocardiogram ST segment depression
Angina unstable	Electrocardiogram ST segment elevation
Arteriogram coronary abnormal	Electrocardiogram ST-T segment abnormal
Arteriosclerosis coronary artery	Electrocardiogram ST-T segment depression
Arteriospasm coronary	Electrocardiogram ST-T segment elevation
Blood creatine phosphokinase abnormal	Exercise electrocardiogram abnormal
Blood creatine phosphokinase increased	Exercise test abnormal
Blood creatine phosphokinase MB abnormal	External counterpulsation
Blood creatine phosphokinase MB increased	Haemorrhage coronary artery
Cardiac enzymes increased	Infarction
Cardiac stress test abnormal	In-stent coronary artery restenosis
Computerised tomogram coronary artery abnormal	Ischaemic cardiomyopathy
Coronary angioplasty	Kounis syndrome
Coronary arterial stent insertion	Microvascular angina
Coronary artery bypass	Myocardial infarction
Coronary artery disease	Myocardial ischaemia
Coronary artery dissection	Myocardial reperfusion injury
Coronary artery embolism	Papillary muscle infarction
Coronary artery insufficiency	Percutaneous coronary intervention
Coronary artery occlusion	Post procedural myocardial infarction
Coronary artery reocclusion	Postinfarction angina
Coronary artery restenosis	Prinzmetal angina
Coronary artery stenosis	Scan myocardial perfusion abnormal
Coronary artery thrombosis	Silent myocardial infarction
Coronary bypass thrombosis	Stress cardiomyopathy
Coronary endarterectomy	Subclavian coronary steal syndrome
Coronary no-reflow phenomenon	Subendocardial ischaemia
Coronary ostial stenosis	Troponin I increased
Coronary revascularisation	Troponin increased
Dissecting coronary artery aneurysm	Troponin T increased
ECG signs of myocardial ischaemia	Vascular graft occlusion

Table 63 FDA Broad MACE SMQ by Category and Preferred Term

Cardiovascular Mortality		
Cardiac arrest	Cardiac fibrillation	Sudden cardiac death
Cardiac death	Cardio-respiratory arrest	Sudden death
Myocardial Infarction		
Acute coronary syndrome	Coronary artery reocclusion	Myocardial reperfusion injury
Acute myocardial infarction	Coronary artery thrombosis	Papillary muscle infarction
Blood creatine phosphokinase abnormal	Coronary bypass thrombosis	Postinfarction angina
Blood creatine phosphokinase increased	Electrocardiogram Q wave abnormal	Post procedural myocardial infarction
Blood creatine phosphokinase MB abnormal	Electrocardiogram ST segment abnormal	Scan myocardial perfusion abnormal
Blood creatine phosphokinase MB increased	Electrocardiogram ST segment elevation	Silent myocardial infarction
Cardiac enzymes increased	Electrocardiogram ST-T segment elevation	Troponin I increased
Coronary artery embolism	Infarction	Troponin increased
Coronary artery occlusion	Myocardial infarction	Troponin T increased
		Vascular graft occlusion
Stroke		
Agnosia	Cerebral artery thrombosis	Monoplegia
Amaurosis fugax	Cerebral haematoma	Moyamoya disease
Angiogram cerebral abnormal	Cerebral haemorrhage	Paralysis
Aphasia	Cerebral haemorrhage foetal	Paralysis flaccid
Balint's syndrome	Cerebral haemorrhage neonatal	Paraparesis
Basal ganglia haemorrhage	Cerebral infarction	Paraplegia
Basilar artery occlusion	Cerebral infarction foetal	Paresis
Basilar artery stenosis	Cerebral ischaemia	Post procedural stroke
Basilar artery thrombosis	Cerebral thrombosis	Precerebral artery occlusion
Brain stem haemorrhage	Cerebral vasoconstriction	Putamen haemorrhage
Brain stem infarction	Cerebral venous thrombosis	Quadriparesis
Brain stem ischaemia	Cerebrovascular accident	Quadriplegia
Brain stem stroke	Cerebrovascular accident prophylaxis	Red blood cells CSF positive
Brain stem thrombosis	Cerebrovascular disorder	Reversible ischemic neurologic deficit
Capsular warning syndrome	Cerebrovascular insufficiency	Ruptured cerebral aneurysm
Carotid aneurysm rupture	Cerebrovascular spasm	Spastic paralysis
Carotid arterial embolus	Cerebrovascular stenosis	Spastic paraplegia
Carotid arteriosclerosis	Charcot-Bouchard microaneurysms	Spinal artery embolism
Carotid artery aneurysm	Diplegia	Spinal cord haemorrhage
Carotid artery bypass	Dysarthria	Spinal epidural haemorrhage
Carotid artery disease	Embolic cerebral infarction	Spinal haematoma
Carotid artery dissection	Embolic stroke	Stroke in evolution
Carotid artery insufficiency	Haematomyelia	Subarachnoid haemorrhage
Carotid artery occlusion	Haemorrhage intracranial	Subarachnoid haemorrhage neonatal
Carotid artery stenosis	Haemorrhagic cerebral infarction	Subdural haemorrhage
Carotid artery stent insertion	Haemorrhagic stroke	Subdural haemorrhage neonatal
Carotid artery thrombosis	Haemorrhagic transformation stroke	Thalamic infarction
Carotid endarterectomy	Hemiparesis	Thalamus haemorrhage
Central pain syndrome	Hemiplegia	Thrombotic cerebral infarction

Table 63 FDA Broad MACE SMQ by Category and Preferred Term (*Continued*)

Stroke (continued)		
Cerebellar artery occlusion	Intra-cerebral aneurysm operation	Thrombotic stroke
Cerebellar artery thrombosis	Intracerebral haematoma evacuation	Transient ischaemic attack
Cerebellar embolism	Intracranial aneurysm	Vascular encephalopathy
Cerebellar haematoma	Intracranial haematoma	Vertebral artery occlusion
Cerebellar haemorrhage	Intraventricular haemorrhage	Vertebral artery stenosis
Cerebellar infarction	Intraventricular hemorrhage neonatal	Vertebral artery thrombosis
Cerebellar ischaemia	Ischaemic cerebral infarction	Vertebrobasilar insufficiency
Cerebral aneurysm ruptured syphilitic	Ischaemic stroke	Visual midline shift syndrome
Cerebral arteriosclerosis	Lacunar infarction	Wallenberg syndrome
Cerebral arteriovenous malformation haemorrhagic	Lateral medullary syndrome	
Cerebral artery embolism	Meningorrhagia	
Cerebral artery occlusion	Millard-Gubler syndrome	
Cerebral artery stenosis	Monoparesis	

Table 64 FDA Custom MACE SMQ by Category and Preferred Terms

Cardiovascular Mortality		
Sudden death	Cardiac death	Cardio-respiratory arrest
Cardiac arrest	Cardiac fibrillation	Sudden cardiac death
Myocardial INFARCTION		
Acute myocardial infarction	Myocardial infarction	Silent myocardial infarction
Coronary artery thrombosis	Papillary muscle infarction	Post procedural myocardial infarction
Stroke		
Basilar artery thrombosis	Cerebral thrombosis	Lateral medullary syndrome
Brain stem infarction	Cerebrovascular accident	Moyamoya disease
Brain stem stroke	Embolic cerebral infarction	Post procedural stroke
Brain stem thrombosis	Embolic stroke	Stroke in evolution
Carotid arterial embolus	Haemorrhagic cerebral infarction	Thalamic infarction
Carotid artery thrombosis	Haemorrhagic stroke	Thrombotic cerebral infarction
Cerebellar infarction	Haemorrhagic transformation stroke	Thrombotic stroke
Cerebral artery embolism	Ischaemic cerebral infarction	Wallenberg syndrome
Cerebral artery thrombosis	Ischaemic stroke	
Cerebral infarction	Lacunar infarction	

Table 65 Psychiatric TME by Subclasses and Preferred Terms

Depression TME Subclass	
Activation syndrome	Dysphoria
Adjustment disorders with depressed mood	Dysthymic disorder
Adjustment disorder with mixed anxiety and depressed mood	Electroconvulsive therapy
	Emotional distress
Affect lability	Feeling guilty
Agitated depression	Feeling of despair
Alcohol abuse	Feelings of worthlessness
Alcohol problem	Impaired self-care
Alcohol rehabilitation	Listless
Alcoholism	Major depression
Anhedonia	Menopausal depression
Antidepressant therapy	Mood altered
Apathy	Mood swings
Blunted affect	Morose
Constricted affect	Negative thoughts
Crying	Neglect of personal appearance
Decreased interest	Psychosocial support
Depressed mood	Psychotherapy
Depression	Self esteem decreased
Depression postoperative	Tearfulness
Depressive symptom	
Suicide/Self-injury TME Subclass	
Completed suicide	Self injurious behaviour
Depression suicidal	Self injurious ideation
Intentional overdose	Suicidal behavior
Intentional self-injury	Suicidal ideation
Multiple drug overdose intentional	Suicide attempt
Poisoning deliberate	
Sleep Disorders TME Subclass	
Dysomnia	Insomnia
Early morning awakening	Middle insomnia
Hypersomnia	Poor quality sleep
Hyposomnia	Somnolence
Initial insomnia	
Anxiety TME Subclass	
Agitation	
Anxiety	
Irritability	

Table 66 Psychosis and Psychotic Disorders SMQ

Preferred Terms	
Acute psychosis	Schizophrenia, disorganised type
Alcoholic psychosis	Schizophrenia, paranoid type
Alice in wonderland syndrome	Schizophrenia, residual type
Brief psychotic disorder with marked stressors	Schizophrenia, undifferentiated type
Brief psychotic disorder without marked stressors	Schizophreniform disorder
Brief psychotic disorder, with postpartum onset	Schizotypal personality disorder
Charles Bonnet syndrome	Senile psychosis
Childhood psychosis	Shared psychotic disorder
Clang associations	Somatic delusion
Cotard's syndrome	Somatic hallucination
Delusion	Tangentiality
Delusion of grandeur	Thought blocking
Delusion of reference	Thought broadcasting
Delusion of replacement	Thought insertion
Delusional disorder, erotomanic type	Thought withdrawal
Delusional disorder, grandiose type	Transient psychosis
Delusional disorder, jealous type	Waxy flexibility
Delusional disorder, mixed type	Abnormal behavior
Delusional disorder, persecutory type	Abulia
Delusional disorder, somatic type	Affect lability
Delusional disorder, unspecified type	Affective disorder
Delusional perception	Alcohol withdrawal syndrome
Delusions, mixed	Anosognosia
Dementia of the Alzheimer's type, with delusions	Apathy
Depressive delusion	Asocial behaviour
Derailment	Bipolar I disorder
Epileptic psychosis	Blunted affect
Erotomanic delusion	Bradyphrenia
Flight of ideas	Catatonia
Hallucination	Childhood disintegrative disorder
Hallucination, auditory	Constricted affect
Hallucination, gustatory	Dyslogia
Hallucination, olfactory	Echolalia
Hallucination, synaesthetic	Echopraxia
Hallucination, tactile	Flat affect
Hallucination, visual	Grandiosity
Hallucinations, mixed	Hypomania
Hypnagogic hallucination	Idioglossia
Hypnopompic hallucination	Illogical thinking
Hysterical psychosis	Inappropriate affect
Ideas of reference	Incoherent
Illusion	Lack of spontaneous speech
Jealous delusion	Logorrhoea
Korsakoff's psychosis alcoholic	Magical thinking
Korsakoff's psychosis non-alcoholic	Major depression
Loose associations	Mania
Neologism	Mutism
Paranoia	Obsessive rumination
Paranoid personality disorder	Perseveration
Paroxysmal perceptual alteration	Poverty of speech
Persecutory delusion	Poverty of thought content
Posturing	Presenile dementia

Table 66 Psychosis and Psychotic Disorders SMQ (*Continued*)

Preferred Terms	
Psychosis postoperative	Pressure of speech
Psychotic behaviour	Senile dementia
Psychotic disorder	Social avoidant behaviour
Psychotic disorder due to a general medical condition	Speech disorder
Reactive psychosis	Suspiciousness
Schizoaffective disorder	Tachyphrenia
Schizoaffective disorder bipolar type	Thinking abnormal
Schizoaffective disorder depressive type	Vascular dementia
Schizophrenia	Verbigeration
Schizophrenia simple	Wernicke-Korsakoff syndrome
Schizophrenia, catatonic type	

Table 67 Cognitive Disorders TME Subclasses and Preferred Terms

TME Subclass	Preferred Terms
Attention	Disturbance in attention, Change in sustained attention
Other cognitive NOS	Borderline mental impairment, Bradyphrenia, Cognitive disorder, Cognitive impairment, Confusional state, Disorientation, Dyscalculia, Judgement impaired, Mental impairment, Thinking abnormal
Memory impairment	Memory impairment, amnesia
Language	Dysarthria, aphasia, difficulty with language, dysphasia

Table 68 Renal Events of Special Interest

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

Table 69 Hepatic Events of Special Interest

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

Table 70 Gallbladder Subtopic, Categories, and Preferred Terms

Subtopic	Category	Preferred Terms
Gallbladder	Cholelithiasis	Cholelithiasis, biliary colic, gallbladder disorder, gallbladder pain, laparoscopic surgery
	Cholecystitis	Cholecystitis, cholecystitis chronic, cholecystitis acute

Table 71 Hypersensitivity Reaction/Skin Rash 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, eosinophilia, hyperventilation, laryngeal inflammation, allergic cough, generalised oedema, oral pruritus, oropharyngeal discomfort, oropharyngeal pain
Skin Reactions	Blistering	Blister, oropharyngeal blistering
	Rash	Rash, pruritus, erythema nodosum, rash erythematous, dermatitis, erythema, dermatitis allergic, rash generalised, rash pruritic, rash maculo-papular, pruritus generalised, drug eruption, rash macular, ulcerative keratitis, rash popular, photosensitivity reaction
	Urticaria	Urticaria
Local Reactions		Eye swelling, local swelling, sneezing, rhinitis allergic, conjunctivitis allergic, eye allergy, eyelid oedema, ocular hyperaemia, eye pruritus, scleral hyperaemia

Table 72 Joint and Muscle Pain Subtopics and Preferred Terms

Subtopic	Preferred Terms
Arthralgia	Arthralgia, meniscus lesion, arthritis, osteoarthritis, gout, bunion, joint crepitation, joint stiffness, joint swelling, rheumatoid arthritis, temporomandibular joint syndrome, arthroscopic surgery, arthroscopy, patellofemoral pain syndrome, periarthritis, facet joint syndrome, knee arthroplasty, knee operation, spinal osteoarthritis
Myalgia	Myalgia, muscle tightness, muscle rupture, muscle spasms, muscle strain, fibromyalgia, muscle swelling
Musculoskeletal Pain	Back pain, pain in extremity, musculoskeletal pain, neck pain, tendonitis, plantar fasciitis, musculoskeletal stiffness, carpal tunnel syndrome, flank pain, intervertebral disc protrusion, rotator cuff syndrome, exostosis, ligament rupture, musculoskeletal chest pain, musculoskeletal discomfort, costochondritis, epicondylitis, groin pain, tendon rupture, trigger finger, bone pain, back disorder, bunion operation, fasciotomy, metatarsal excision, myositis, osteotomy, tendon disorder, tendon pain, tenotomy, dupuytren's contracture, fasciitis, limb discomfort, tenosynovitis stenosans, tenosynovitis, medial tibial stress syndrome, ligament sprain, carpal tunnel decompression

Table 73 Sexual Dysfunction Subtopics and Preferred Terms

Subtopic	Preferred Terms
Male Events	Erectile dysfunction, erection increased
Unspecified	Libido decreased, anorgasmia, sexual dysfunction, loss of libido

Appendix 8 Summary of Adverse Events and Vital Signs by Subgroups

Table 74 Summary of Adverse Events by Subgroup: Primary Dataset, Double-Blind Treatment Phase

Category Subgroup	n (%) of Patients with at least 1 event							
	AE				AE leading to discontinuation			
	Placebo (N=1515)		Total NB (N=3239)		Placebo (N=1515)		Total NB (N=3239)	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Sex								
Male	268	202 (75.4%)	549	458 (83.4%)	268	31 (11.6%)	549	93 (16.9%)
Female	1247	935 (75.0%)	2690	2311 (85.9%)	1247	150 (12.0%)	2690	678 (25.2%)
Age								
18-44	686	483 (70.4%)	1443	1185 (82.1%)	686	78 (11.4%)	1443	306 (21.2%)
45-64	797	629 (78.9%)	1734	1523 (87.8%)	797	99 (12.4%)	1734	441 (25.4%)
≥ 65	32	25 (78.1%)	62	61 (98.4%)	32	4 (12.5%)	62	24 (38.7%)
Race								
White	1193	892 (74.8%)	2477	2128 (85.9%)	1193	142 (11.9%)	2477	555 (22.4%)
Black /African American	261	200 (76.6%)	614	517 (84.2%)	261	28 (10.7%)	614	169 (27.5%)
Other	61	45 (73.8%)	148	124 (83.8%)	61	11 (18.0%)	148	47 (31.8%)
Ethnicity								
Hispanic/Latino	166	109 (65.7%)	306	259 (84.6%)	166	20 (12.0%)	306	90 (29.4%)
Not Hispanic/Latino	1349	1028 (76.2%)	2933	2510 (85.6%)	1349	161 (11.9%)	2933	681 (23.2%)
≥5% Responder								
Yes	287	243 (84.7%)	1351	1207 (89.3%)	287	21 (7.3%)	1351	94 (7.0%)
No	1228	894 (72.8%)	1888	1562 (82.7%)	1228	160 (13.0%)	1888	677 (35.9%)
Smoking Status at Baseline								
Yes	131	89 (67.9%)	263	211 (80.2%)	131	15 (11.5%)	263	51 (19.4%)
No	1384	1048 (75.7%)	2976	2558 (86.0%)	1384	166 (12.0%)	2976	720 (24.2%)

Table 74 Summary of Adverse Events by Subgroup: Primary Dataset, Double-Blind Treatment Phase (*Continued*)

Category Subgroup	n (%) of Patients with at least 1 event							
	AE				AE leading to discontinuation			
	Placebo (N=1515)		Total NB (N=3239)		Placebo (N=1515)		Total NB (N=3239)	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Antihypertensive Medication Use at Baseline								
Yes	359	296 (82.5%)	792	705 (89.0%)	359	51 (14.2%)	792	193 (24.4%)
No	1156	841 (72.8%)	2447	2064 (84.3%)	1156	130 (11.2%)	2447	578 (23.6%)
Obesity Class at Baseline								
BMI <30 kg/m^2	31	24 (77.4%)	85	74 (87.1%)	31	5 (16.1%)	85	22 (25.9%)
BMI ≥30 and <35 kg/m^2	547	399 (72.9%)	1234	1054 (85.4%)	547	67 (12.2%)	1234	312 (25.3%)
BMI ≥35 and <40 kg/m^2	596	453 (76.0%)	1135	959 (84.5%)	596	71 (11.9%)	1135	267 (23.5%)
BMI ≥40 kg/m^2	341	261 (76.5%)	785	682 (86.9%)	341	38 (11.1%)	785	170 (21.7%)

Table 75 Summary of Systolic Blood Pressure Outlier Values by Subgroup: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)				Total NB (N=3239)			
Category Subgroup		**≥140 mm Hg**	**≥160 mm Hg**	**≥10 mm Hg over BL**		**≥140 mm Hg**	**≥160 mm Hg**	**≥10 mm Hg over BL**
	N[a]	**n (%)**	**n (%)**	**n (%)**	**N[a]**	**n (%)**	**n (%)**	**n (%)**
Sex								
Male	257	26 (10.1%)	0	55 (21.4%)	500	60 (12.0%)	2 (0.4%)	142 (28.4%)
Female	1162	30 (2.6%)	2 (0.2%)	209 (18.0%)	2312	120 (5.2%)	3 (0.1%)	561 (24.3%)
Age								
18-44	637	10 (1.6%)	0	124 (19.5%)	1231	36 (2.9%)	1 (<0.1%)	291 (23.6%)
45-64	750	40 (5.3%)	1 (0.1%)	130 (17.3%)	1524	130 (8.5%)	4 (0.3%)	394 (25.9%)
≥65	32	6 (18.8%)	1 (3.1%)	10 (31.3%)	57	14 (24.6%)	0	18 (31.6%)
Race								
White	1122	46 (4.1%)	2 (0.2%)	214 (19.1%)	2186	133 (6.1%)	3 (0.1%)	523 (23.9%)
Black or African American	242	8 (3.3%)	0	43 (17.8%)	499	41 (8.2%)	1 (0.2%)	148 (29.7%)
Other	55	2 (3.6%)	0	7 (12.7%)	127	6 (4.7%)	1 (0.8%)	32 (25.2%)
Ethnicity								
Hispanic or Latino	152	4 (2.6%)	0	26 (17.1%)	248	18 (7.3%)	1 (0.4%)	59 (23.8%)
Not Hispanic or Latino	1267	52 (4.1%)	2 (0.2%)	238 (18.8%)	2564	162 (6.3%)	4 (0.2%)	644 (25.1%)
5% Responder								
Yes	287	10 (3.5%)	0	42 (14.6%)	1351	69 (5.1%)	0	323 (23.9%)
No	1132	46 (4.1%)	2 (0.2%)	222 (19.6%)	1461	111 (7.6%)	5 (0.3%)	380 (26.0%)
Smoking Status at baseline								
Yes	114	7 (6.1%)	0	28 (24.6%)	221	13 (5.9%)	0	49 (22.2%)
No	1305	49 (3.8%)	2 (0.2%)	236 (18.1%)	2591	167 (6.4%)	5 (0.2%)	654 (25.2%)
Antihypertensive Medication Use at Baseline								
Yes	342	26 (7.6%)	1 (0.3%)	71 (20.8%)	705	89 (12.6%)	4 (0.6%)	208 (29.5%)
No	1077	30 (2.8%)	1 (<0.1%)	193 (17.9%)	2107	91 (4.3%)	1 (<0.1%)	495 (23.5%)

Table 75 Summary of Systolic Blood Pressure Outlier Values by Subgroup: Primary Dataset, Double-Blind Treatment Phase (*Continued*)

	Placebo (N=1515)				Total NB (N=3239)			
Category Subgroup		**≥140 mm Hg**	**≥160 mm Hg**	**≥10 mm Hg over BL**		**≥140 mm Hg**	**≥160 mm Hg**	**≥10 mm Hg over BL**
	N[a]	**n (%)**	**n (%)**	**n (%)**	**N[a]**	**n (%)**	**n (%)**	**n (%)**
Obesity Class at Baseline								
BMI <30 kg/m^2	30	4 (13.3%)	0	9 (30.0%)	72	6 (8.3%)	1 (1.4%)	14 (19.4%)
BMI ≥30 and <35 kg/m^2	515	14 (2.7%)	1 (0.2%)	101 (19.6%)	1067	55 (5.2%)	1 (<0.1%)	252 (23.6%)
BMI ≥35 and <40 kg/m^2	548	27 (4.9%)	1 (0.2%)	98 (17.9%)	990	63 (6.4%)	2 (0.2%)	254 (25.7%)
BMI ≥40 kg/m^2	326	11 (3.4%)	0	56 (17.2%)	683	56 (8.2%)	1 (0.1%)	183 (26.8%)
Diabetes								
Yes	161	16 (9.9%)	1 (0.6%)	42 (26.1%)	293	50 (17.1%)	3 (1.0%)	85 (29.0%)
No	1258	40 (3.2%)	1 (<0.1%)	222 (17.6%)	2519	130 (5.2%)	2 (<0.1%)	618 (24.5%)
Cardiovascular Medical History								
Yes	418	35 (8.4%)	1 (0.2%)	82 (19.6%)	818	101 (12.3%)	4 (0.5%)	234 (28.6%)
No	1001	21 (2.1%)	1 (<0.1%)	182 (18.2%)	1994	79 (4.0%)	1 (<0.1%)	469 (23.5%)
Arrhythmia Medical History								
Yes	50	4 (8.0%)	1 (2.0%)	11 (22.0%)	85	8 (9.4%)	0	23 (27.1%)
No	1369	52 (3.8%)	1 (<0.1%)	253 (18.5%)	2727	172 (6.3%)	5 (0.2%)	680 (24.9%)
Ischemic Medical History								
Yes	22	4 (18.2%)	0	5 (22.7%)	35	6 (17.1%)	0	11 (31.4%)
No	1397	52 (3.7%)	2 (0.1%)	259 (18.5%)	2777	174 (6.3%)	5 (0.2%)	692 (24.9%)
Presence of Dyslipidemia								
Yes	751	39 (5.2%)	2 (0.3%)	145 (19.3%)	1554	120 (7.7%)	4 (0.3%)	388 (25.0%)
No	668	17 (2.5%)	0	119 (17.8%)	1258	60 (4.8%)	1 (<0.1%)	315 (25.0%)

At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
a. Number of patients with at least 1 post-Baseline measurement.
Abbreviations: BL=baseline; BMI=body mass index; Total NB=all doses of combination naltrexone and bupropion treatment.

Table 76 Summary of Diastolic Blood Pressure Outlier Values by Subgroup: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)				Total NB (N=3239)			
		≥90 mm Hg	≥100 mm Hg	≥5 mm Hg over BL		≥90 mm Hg	≥100 mm Hg	≥5 mm Hg over BL
Subgroup	**N[a]**	**n (%)**	**n (%)**	**n (%)**	**N[a]**	**n (%)**	**n (%)**	**n (%)**
Sex								
Male	257	26 (10.1%)	4 (1.6%)	83 (32.3%)	500	55 (11.0%)	5 (1.0%)	195 (39.0%)
Female	1162	38 (3.3%)	2 (0.2%)	323 (27.8%)	2312	125 (5.4%)	7 (0.3%)	844 (36.5%)
Age								
18-44	637	30 (4.7%)	2 (0.3%)	194 (30.5%)	1231	76 (6.2%)	5 (0.4%)	486 (39.5%)
45-64	750	33 (4.4%)	4 (0.5%)	200 (26.7%)	1524	102 (6.7%)	7 (0.5%)	532 (34.9%)
≥65	32	1 (3.1%)	0	12 (37.5%)	57	2 (3.5%)	0	21 (36.8%)
Race								
White	1122	43 (3.8%)	5 (0.4%)	324 (28.9%)	2186	120 (5.5%)	5 (0.2%)	778 (35.6%)
Black or African American	242	17 (7.0%)	1 (0.4%)	69 (28.5%)	499	49 (9.8%)	6 (1.2%)	214 (42.9%)
Other	55	4 (7.3%)	0	13 (23.6%)	127	11 (8.7%)	1 (0.8%)	47 (37.0%)
Ethnicity								
Hispanic or Latino	152	6 (3.9%)	0	44 (28.9%)	248	19 (7.7%)	2 (0.8%)	107 (43.1%)
Not Hispanic or Latino	1267	58 (4.6%)	6 (0.5%)	362 (28.6%)	2564	161 (6.3%)	10 (0.4%)	932 (36.3%)
5% Responder								
Yes	287	12 (4.2%)	2 (0.7%)	67 (23.3%)	1351	77 (5.7%)	6 (0.4%)	502 (37.2%)
No	1132	52 (4.6%)	4 (0.4%)	339 (29.9%)	1461	103 (7.0%)	6 (0.4%)	537 (36.8%)
Smoking Status at baseline								
Yes	114	4 (3.5%)	0	37 (32.5%)	221	12 (5.4%)	1 (0.5%)	77 (34.8%)
No	1305	60 (4.6%)	6 (0.5%)	369 (28.3%)	2591	168 (6.5%)	11 (0.4%)	962 (37.1%)
Antihypertensive Medication Use at Baseline								
Yes	342	25 (7.3%)	2 (0.6%)	100 (29.2%)	705	59 (8.4%)	4 (0.6%)	281 (39.9%)
No	1077	39 (3.6%)	4 (0.4%)	306 (28.4%)	2107	121 (5.7%)	8 (0.4%)	758 (36.0%)

Table 76 Summary of Diastolic Blood Pressure Outlier Values by Subgroup: Primary Dataset, Double-Blind Treatment Phase (*Continued*)

	Placebo (N=1515)				Total NB (N=3239)			
		≥90 mm Hg	≥100 mm Hg	≥5 mm Hg over BL		≥90 mm Hg	≥100 mm Hg	≥5 mm Hg over BL
Subgroup	**N[a]**	**n (%)**	**n (%)**	**n (%)**	**N[a]**	**n (%)**	**n (%)**	**n (%)**
Obesity Class at Baseline								
BMI <30 kg/m^2	30	1 (3.3%)	0	7 (23.3%)	72	5 (6.9%)	0	19 (26.4%)
BMI ≥30 and <35 kg/m^2	515	16 (3.1%)	2 (0.4%)	145 (28.2%)	1067	50 (4.7%)	4 (0.4%)	386 (36.2%)
BMI ≥35 and <40 kg/m^2	548	32 (5.8%)	3 (0.5%)	160 (29.2%)	990	78 (7.9%)	4 (0.4%)	362 (36.6%)
BMI ≥40 kg/m^2	326	15 (4.6%)	1 (0.3%)	94 (28.8%)	683	47 (6.9%)	4 (0.6%)	272 (39.8%)
Diabetes								
Yes	161	10 (6.2%)	1 (0.6%)	52 (32.3%)	293	19 (6.5%)	3 (1.0%)	109 (37.2%)
No	1258	54 (4.3%)	5 (0.4%)	354 (28.1%)	2519	161 (6.4%)	9 (0.4%)	930 (36.9%)
Cardiovascular Medical History								
Yes	418	30 (7.2%)	3 (0.7%)	123 (29.4%)	818	72 (8.8%)	6 (0.7%)	322 (39.4%)
No	1001	34 (3.4%)	3 (0.3%)	283 (28.3%)	1994	108 (5.4%)	6 (0.3%)	717 (36.0%)
Arrhythmia Medical History								
Yes	50	2 (4.0%)	0	16 (32.0%)	85	2 (2.4%)	0	33 (38.8%)
No	1369	62 (4.5%)	6 (0.4%)	390 (28.5%)	2727	178 (6.5%)	12 (0.4%)	1006 (36.9%)
Ischemic Medical History								
Yes	22	1 (4.5%)	0	4 (18.2%)	35	2 (5.7%)	1 (2.9%)	13 (37.1%)
No	1397	63 (4.5%)	6 (0.4%)	402 (28.8%)	2777	178 (6.4%)	11 (0.4%)	1026 (36.9%)
Presence of Dyslipidemia								
Yes	751	39 (5.2%)	3 (0.4%)	214 (28.5%)	1554	101 (6.5%)	9 (0.6%)	570 (36.7%)
No	668	25 (3.7%)	3 (0.4%)	192 (28.7%)	1258	79 (6.3%)	3 (0.2%)	469 (37.3%)

At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
a. Number of patients with at least 1 post-Baseline measurement.
Abbreviations: BL=baseline; BMI=body mass index; Total NB=all doses of combination naltrexone and bupropion treatment.

Table 77 Summary of Heart Rate Outlier Values by Subgroup: Primary Dataset, Double-Blind Treatment Phase

	Placebo (N=1515)				Total NB (N=3239)			
		≥100 bpm	≥110 bpm	≥10 bpm over BL		≥100 bpm	≥110 bpm	≥10 bpm over BL
Subgroup	**N[a]**	**n (%)**	**n (%)**	**n (%)**	**N[a]**	**n (%)**	**n (%)**	**n (%)**
Sex								
Male	257	1 (0.4%)	0	53 (20.6%)	500	4 (0.8%)	0	147 (29.4%)
Female	1162	6 (0.5%)	1 (<0.1%)	216 (18.6%)	2312	23 (1.0%)	0	594 (25.7%)
Age								
18-44	637	4 (0.6%)	1 (0.2%)	140 (22.0%)	1231	13 (1.1%)	0	378 (30.7%)
45-64	750	3 (0.4%)	0	120 (16.0%)	1524	13 (0.9%)	0	349 (22.9%)
≥65	32	0	0	9 (28.1%)	57	1 (1.8%)	0	14 (24.6%)
Race								
White	1122	5 (0.4%)	1 (<0.1%)	209 (18.6%)	2186	15 (0.7%)	0	556 (25.4%)
Black or African American	242	2 (0.8%)	0	55 (22.7%)	499	10 (2.0%)	0	145 (29.1%)
Other	55	0	0	5 (9.1%)	127	2 (1.6%)	0	40 (31.5%)
Ethnicity								
Hispanic or Latino	152	0	0	23 (15.1%)	248	2 (0.8%)	0	74 (29.8%)
Not Hispanic or Latino	1267	7 (0.6%)	1 (<0.1%)	246 (19.4%)	2564	25 (1.0%)	0	667 (26.0%)
5% Responder								
Yes	287	1 (0.3%)	0	41 (14.3%)	1351	9 (0.7%)	0	382 (28.3%)
No	1132	6 (0.5%)	1 (<0.1%)	228 (20.1%)	1461	18 (1.2%)	0	359 (24.6%)
Smoking Status at baseline								
Yes	114	1 (0.9%)	0	17 (14.9%)	221	6 (2.7%)	0	45 (20.4%)
No	1305	6 (0.5%)	1 (<0.1%)	252 (19.3%)	2591	21 (0.8%)	0	696 (26.9%)
Antihypertensive Medication Use at Baseline								
Yes	342	2 (0.6%)	1 (0.3%)	63 (18.4%)	705	10 (1.4%)	0	172 (24.4%)
No	1077	5 (0.5%)	0	206 (19.1%)	2107	17 (0.8%)	0	569 (27.0%)

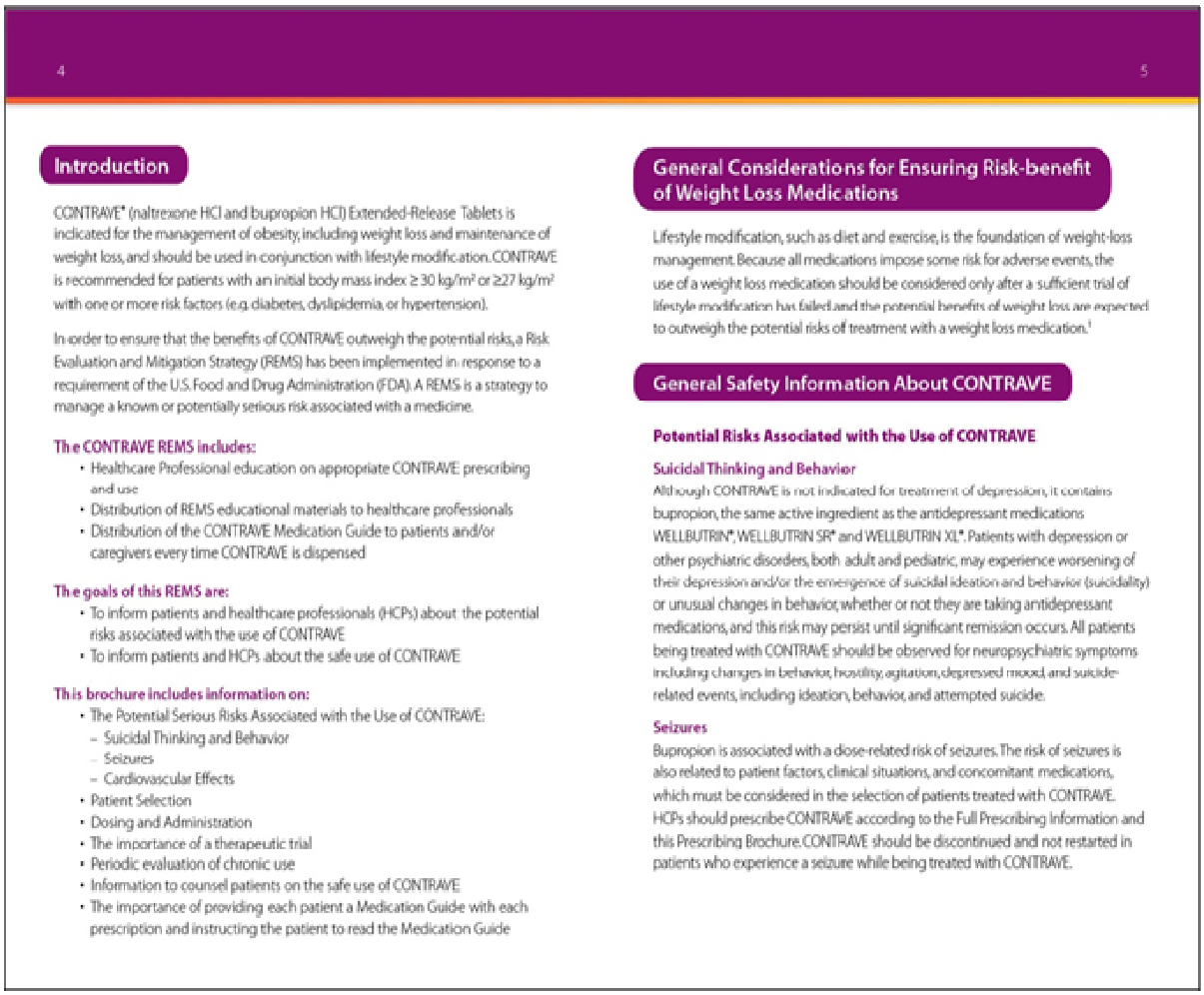
Table 77 Summary of Heart Rate Outlier Values by Subgroup: Primary Dataset, Double-Blind Treatment Phase (*Continued*)

	Placebo (N=1515)				Total NB (N=3239)			
		≥100 bpm	≥110 bpm	≥10 bpm over BL		≥100 bpm	≥110 bpm	≥10 bpm over BL
Subgroup	**N[a]**	**n (%)**	**n (%)**	**n (%)**	**N[a]**	**n (%)**	**n (%)**	**n (%)**
Obesity Class at Baseline								
BMI <30 kg/m^2	30	0	0	6 (20.0%)	72	2 (2.8%)	0	24 (33.3%)
BMI ≥30 and <35 kg/m^2	515	3 (0.6%)	0	106 (20.6%)	1067	6 (0.6%)	0	296 (27.7%)
BMI ≥35 and <40 kg/m^2	548	3 (0.5%)	1 (0.2%)	92 (16.8%)	990	13 (1.3%)	0	246 (24.8%)
BMI ≥40 kg/m^2	326	1 (0.3%)	0	65 (19.9%)	683	6 (0.9%)	0	175 (25.6%)
Diabetes								
Yes	161	2 (1.2%)	0	35 (21.7%)	293	3 (1.0%)	0	68 (23.2%)
No	1258	5 (0.4%)	1 (<0.1%)	234 (18.6%)	2519	24 (1.0%)	0	673 (26.7%)
Cardiovascular Medical History								
Yes	418	1 (0.2%)	0	79 (18.9%)	818	11 (1.3%)	0	199 (24.3%)
No	1001	6 (0.6%)	1 (<0.1%)	190 (19.0%)	1994	16 (0.8%)	0	542 (27.2%)
Arrhythmia Medical History								
Yes	50	0	0	9 (18.0%)	85	0	0	23 (27.1%)
No	1369	7 (0.5%)	1 (<0.1%)	260 (19.0%)	2727	27 (1.0%)	0	718 (26.3%)
Ischemic Medical History								
Yes	22	0	0	7 (31.8%)	35	0	0	8 (22.9%)
No	1397	7 (0.5%)	1 (<0.1%)	262 (18.8%)	2777	27 (1.0%)	0	733 (26.4%)
Presence of Dyslipidemia								
Yes	751	1 (0.1%)	0	134 (17.8%)	1554	12 (0.8%)	0	391 (25.2%)
No	668	6 (0.9%)	1 (0.1%)	135 (20.2%)	1258	15 (1.2%)	0	350 (27.8%)

At least two consecutive treatment-emergent values or a single treatment-emergent value if last.
a. Number of patients with at least 1 post-Baseline measurement.
Abbreviations: BL=baseline; Total NB=all doses of combination naltrexone and bupropion treatment.

Appendix 9 Risk Mitigation Materials

Figure 44 Draft Prescribing Brochure (sample page)



4 5

Introduction

CONTRAVE® (naltrexone HCl and bupropion HCl) Extended-Release Tablets is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification. CONTRAVE is recommended for patients with an initial body mass index ≥ 30 kg/m² or ≥27 kg/m² with one or more risk factors (e.g. diabetes, dyslipidemia, or hypertension).

In order to ensure that the benefits of CONTRAVE outweigh the potential risks, a Risk Evaluation and Mitigation Strategy (REMS) has been implemented in response to a requirement of the U.S. Food and Drug Administration (FDA). A REMS is a strategy to manage a known or potentially serious risk associated with a medicine.

The CONTRAVE REMS includes:

- Healthcare Professional education on appropriate CONTRAVE prescribing and use
- Distribution of REMS educational materials to healthcare professionals
- Distribution of the CONTRAVE Medication Guide to patients and/or caregivers every time CONTRAVE is dispensed

The goals of this REMS are:

- To inform patients and healthcare professionals (HCPs) about the potential risks associated with the use of CONTRAVE
- To inform patients and HCPs about the safe use of CONTRAVE

This brochure includes information on:

- The Potential Serious Risks Associated with the Use of CONTRAVE:
  - Suicidal Thinking and Behavior
  - Seizures
  - Cardiovascular Effects
- Patient Selection
- Dosing and Administration
- The importance of a therapeutic trial
- Periodic evaluation of chronic use
- Information to counsel patients on the safe use of CONTRAVE
- The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read the Medication Guide

General Considerations for Ensuring Risk-benefit of Weight Loss Medications

Lifestyle modification, such as diet and exercise, is the foundation of weight-loss management. Because all medications impose some risk for adverse events, the use of a weight loss medication should be considered only after a sufficient trial of lifestyle modification has failed and the potential benefits of weight loss are expected to outweigh the potential risks of treatment with a weight loss medication.[1]

General Safety Information About CONTRAVE

Potential Risks Associated with the Use of CONTRAVE

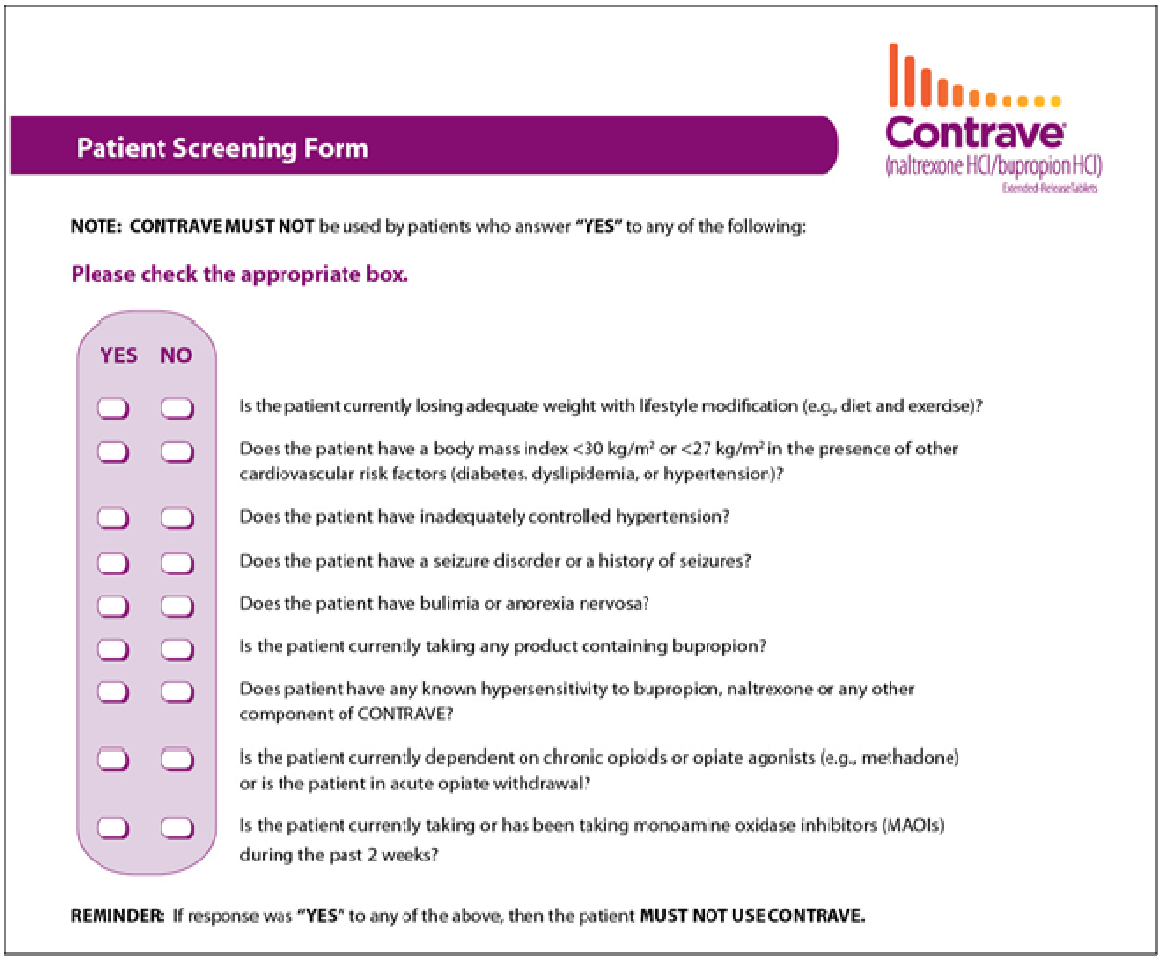
Suicidal Thinking and Behavior

Although CONTRAVE is not indicated for treatment of depression, it contains bupropion, the same active ingredient as the antidepressant medications WELLBUTRIN®, WELLBUTRIN SR® and WELLBUTRIN XL®. Patients with depression or other psychiatric disorders, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. All patients being treated with CONTRAVE should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide.

Seizures

Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in the selection of patients treated with CONTRAVE. HCPs should prescribe CONTRAVE according to the Full Prescribing Information and this Prescribing Brochure. CONTRAVE should be discontinued and not restarted in patients who experience a seizure while being treated with CONTRAVE.

Figure 45 Draft Patient Screening Form



Patient Screening Form

Contrave (naltrexone HCl/bupropion HCl) Extended-Release Tablets

NOTE: CONTRAVE MUST NOT be used by patients who answer **"YES"** to any of the following:

Please check the appropriate box.

YES	NO	
☐	☐	Is the patient currently losing adequate weight with lifestyle modification (e.g., diet and exercise)?
☐	☐	Does the patient have a body mass index <30 kg/m² or <27 kg/m² in the presence of other cardiovascular risk factors (diabetes, dyslipidemia, or hypertension)?
☐	☐	Does the patient have inadequately controlled hypertension?
☐	☐	Does the patient have a seizure disorder or a history of seizures?
☐	☐	Does the patient have bulimia or anorexia nervosa?
☐	☐	Is the patient currently taking any product containing bupropion?
☐	☐	Does patient have any known hypersensitivity to bupropion, naltrexone or any other component of CONTRAVE?
☐	☐	Is the patient currently dependent on chronic opioids or opiate agonists (e.g., methadone) or is the patient in acute opiate withdrawal?
☐	☐	Is the patient currently taking or has been taking monoamine oxidase inhibitors (MAOIs) during the past 2 weeks?

REMINDER: If response was **"YES"** to any of the above, then the patient **MUST NOT USE CONTRAVE.**

Figure 46 Draft Contrave REMS Web Site