CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200063Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 200063/0041	**Submission Date(s):** 12/11/2013
Brand Name	CONTRAVE®
Generic Name	Naltrexone Hydrochloride and Bupropion Hydrochloride in combination
Clinical Pharmacology Reviewer	Manoj Khurana, Ph.D.
Clinical Pharmacology Team Leader	Immo Zadezensky, Ph.D.
OCP Division	Clinical Pharmacology - 2
OND Division	Metabolic and Endocrine Products
Sponsor	Orexigen Therapeutics
Submission Type; Code	Response to Agency's 01/31/2011 Complete Response Letter
Formulation; Strength(s)	Sustained-release trilayer tablets for oral administration; Naltrexone 8 mg/ Bupropion 90 mg
Indication	An adjunct therapy to diet and exercise to improve glycemic control in subjects with type 2 diabetes.

1. Executive Summary

Orexigen Therapeutics (the Sponsor) has submitted a response to the Agency's Complete Response (CR) Letter (*Dated 31st January, 2011*). The purpose of this submission is to address the approval deficiency noted in the CR letter stating that before this application could be approved, the Sponsor must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events (MACE) in overweight and obese subjects treated with Contrave does not adversely affect the drug's benefit-risk profile.

CONTRAVE® (hereafter CONTRAVE or NB) (b) (4) Tablets are proposed for the treatment of obesity and weight management. CONTRAVE is a fixed-dose combination drug product containing two active pharmaceutical ingredients, naltrexone hydrochloride (hereafter naltrexone or N**)** and bupropion hydrochloride **(**hereafter bupropion or B). Naltrexone is a μ (mu) opioid antagonist and bupropion is a dopamine (DA) and norepinephrine (NE) reuptake inhibitor.

Since both active ingredients are approved in the US for use in other indications, this application was submitted by the sponsor as a 505(b)(2) NDA. The sponsor has referenced pertinent information from approved US prescribing information for ReVia® (naltrexone hydrochloride; NDA 18-932) and Wellbutrin SR® (bupropion hydrochloride; NDA 20-358).

Each CONTRAVE tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and claimed to be a (b) (4) tablet. A rapidly dissolving inert layer separates the two drug layers. CONTRAVE will be available as one combination dosage strength tablet:

- CONTRAVE® 8/90, (naltrexone HCL 8 mg/bupropion HCL 90 mg) tablet (hereafter NB 8/90 mg)

Sponsor is not seeking approval of 4/90 mg tablet, (naltrexone HCL 4 mg/bupropion HCL 90 mg) tablet strength proposed with the original NDA submission.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the Complete Response in support of NDA 200063 for CONTRAVE® and found it acceptable. OCP has the following recommendations:

- The current bupropion and naltrexone product labels indicate a potential for significant increase in exposure of bupropion/naltrexone and its metabolites, although to a different magnitude for each of these components in subjects with hepatic or renal impairment. However, in the context of CONTRAVE, the information from individual product labels is limited from a quantitative perspective in precisely guiding the dosing of CONTRAVE across varying degree of hepatic or renal impairment. OCP recommends that further information on these two specific populations be collected in post-marketing studies, meanwhile considering a restricted labeling to ensure safe use of the product.
- An *in-vitro* drug-drug interaction (DDI) study was conducted by the sponsor to evaluate whether naltrexone, bupropion, and their respective metabolites inhibit Organic Cation Transporter 2 (OCT2), which is involved in the tubular secretion

of several drugs and creatinine. The *in-vitro* study results showed that bupropion and its metabolites inhibit OCT2 (Free Cmax/IC50 >0.1 for threohydro-, erythrohydro-bupropion combined), and suggest that clinically relevant interaction through inhibition of OCT2 could occur at therapeutic bupropion doses. Therefore, OCP recommends describing the sponsor's *in vitro* DDI study results in the label with caution on concomitant use of OCT2 substrates with CONTRAVE, and that an *in vivo* evaluation of DDI potential will further help in appropriate labeling of CONTRAVE.

1.2 PHASE IV COMMITMENTS

1) Evaluate the effect of hepatic impairment on pharmacokinetics of naltrexone, bupropion and respective major metabolites (6-beta naltrexol, hydroxybupropion, threohydrobupropion, erythrohydrobupropion) from CONTRAVE formulation. (PMC1, see Attachment 3.1.1)
2) Evaluate the effect of renal impairment on pharmacokinetics of naltrexone, bupropion and respective major metabolites (6-beta naltrexol, hydroxybupropion, threohydrobupropion, erythrohydrobupropion) from CONTRAVE formulation. (PMC2, see Attachment 3.1.2)
3) Conduct a drug-drug interaction study of CONTRAVE with an organic cation transporter-2 (OCT2) substrate, such as metformin. (PMC3, see Attachment 3.1.3)

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

This submission included the Data Monitoring Committee (DMC) Open and Closed Reports from the planned interim analysis of ongoing Study NB-CVOT, as agreed to in the January 2013 Type C meeting and with a commitment to provide the interim analysis clinical study report within 60 days. Sponsor also submitted the pediatric study plan for CONTRAVE.

While we defer the acceptability of the cardio-vascular safety data to the safety statistical reviewer and the clinical reviewer, this review captures the final labeling changes and updated thinking on some of the issues highlighted in the original clinical pharmacology review (*see Clinical Pharmacology Review by Dr. Manoj Khurana in DARRTS, dated 12/23/2010*).

1. **Use in Hepatic Impairment:** The effect of hepatic impairment on pharmacokinetics of bupropion and naltrexone from CONTRAVE is not fully understood. Bupropion undergoes extensive metabolism in liver to hydroxybupropion (AUC based Metabolite-to-parent ratio of 12 at steady-state), threohydrobupropion (AUC based Metabolite-to-parent ratio of 4 at steady-state), and erythrohydrobupropion (AUC based Metabolite-to-parent ratio of 1 at steady-state). Orally administered naltrexone is metabolized extensively by non-CYP pathways (aldo-keto-reductases) to 6-beta naltrexol (AUC based Metabolite-to-parent ratio of 30 at steady-state). Bupropion and metabolites as well as naltrexone and its metabolite are also renally excreted. The currently available information in bupropion and naltrexone product labels indicates a potential for significant increase in exposure of bupropion/naltrexone and its metabolites, although to a different magnitude for each of these components.

A dose based comparison for the available margin is presented in the following table:

Component	CONTRAVE total daily dose	Recommended Daily Dose	Fold Margin
Naltrexone	32 mg	50 mg	~1.5
Bupropion	360 mg	300 mg / Seizure Risk increased for 400 mg total dose	~1.1

The current information on effect of hepatic impairment (HI) on PK of naltrexone and bupropion and recommendations from the approved product labels is summarized in the table below:

Population	Effect on Naltrexone	Effect on Bupropion	Current Approved Label Language
Alcoholic liver disease	-	1.53 – 1.57 fold higher AUC	Wellbutrin®: 75 mg/day in moderate/severe HI
Mild-to-severe cirrhosis	-	1.7 fold higher - Cmax , 3.1 fold higher AUC	Wellbutrin-SR®: 100 mg/day or 150 mg every other day (also included in **Zyban®**) in moderate/severe
Compensated and decompensated liver cirrhosis	5 – 10 fold higher AUC	-	Use with caution in HI (ReVia®)
Mild and Moderate Hepatic Impairment	On average, 1.9 fold higher Cmax and 1.1 fold higher AUC in Mild HI, 0.5 fold lower Cmax and similar AUC (More variability)*	-	Vivitrol® (Injectable Naltrrexone IM) – "Dose adjustment is not required in subjects with mild or moderate hepatic impairment." Not recommended for use in severe HI due to risk of coagulation*.

***NDA 21-897 Clinical Pharmacology Review (http://www.accessdata fda.gov/drugsatfda_docs/nda/2006/021897s000_ClinPharmR.pdf)**

However, collectively the information is limited from a quantitative perspective in precisely guiding the CONTRAVE dosing across varying degree of hepatic impairment. Further, the risk of seizures with bupropion is higher for 400 mg daily dose (Lack of margin for 360 mg/day dose for CONTRAVE). Therefore, anchoring the dosing decision to bupropion, CONTRAVE can be administered at a dose of one tablet (8mg naltrexone/90 mg bupropion) daily in patients with any degree of hepatic impairment. A systematic evaluation of PK in patients with mild, moderate, and severe hepatic impairment will further help in guiding better dosing decision for CONTRAVE. Therefore, OCP is recommending a PMC that requires sponsor to characterize the systematic evaluation of PK of CONTRAVE in subjects with mild, moderate, and severe hepatic impairment.

2. **Use in Renal Impairment:** The effect of renal impairment on pharmacokinetics of bupropion and naltrexone from CONTRAVE is not fully understood. In healthy subjects, the systemic exposure of metabolite is higher for hydroxybupropion (AUC based Metabolite-to-parent ratio of 12 at steady-state), threohydrobupropion (AUC based Metabolite-to-parent ratio of 4 at steady-state), and erythrohydrobupropion (AUC based Metabolite-to-parent ratio of 1 at steady-state). Similarly, for orally administered naltrexone systemic exposures of 6-beta naltrexol are higher than naltrexone (AUC based Metabolite-to-parent ratio of 30 at steady-state). Bupropion and metabolites as well as naltrexone and its metabolite are renally excreted. The current bupropion and naltrexone product labels indicate a potential for significant accumulation of bupropion/naltrexone and its metabolites in the presence of renal impairment, although to a different magnitude for each of these components.

   The current information on effect of renal impairment on PK of naltrexone and bupropion and recommendations from the approved product labels is summarized in the table below:

Population	Effect on Naltrexone	Effect on Bupropion*	Current Labels
Moderate-severe RI	No information but Naltrexone and 6-beta naltrexol is renally excreted and expected to accumulate	2-fold higher AUC	Reduced dose and/or dosing frequency (Bupropion) Use with Caution (Naltrexone)
End-stage Renal Disease	"In a study of 7 patients with end-stage renal disease requiring dialysis, peak plasma concentrations of naltrexone were elevated several-fold compared to healthy subjects."	2-3 fold higher AUC of metabolites	

However, the information is limited from a quantitative perspective in precisely guiding the dosing across varying degree of renal impairment. Further, the risk of seizures with bupropion is increased for 400 mg daily dose (Lack of margin for 360 mg/day dose for CONTRAVE). Therefore, anchoring the dosing decision to bupropion, CONTRAVE can be administered at a dose of two tablets (one each 8mg naltrexone/90 mg bupropion tablet in the morning and evening) daily in patients with moderate or severe renal impairment. No dose adjustment is required in patients with mild renal impairment. Patients with mild renal impairment were included in safety and efficacy trials of CONTRAVE. CONTRAVE use is not recommended in patients with end stage renal disease. A systematic evaluation of PK in patients with mild, moderate, and severe hepatic impairment will further help in guiding better dosing decision for CONTRAVE. A systematic evaluation of PK in patients with mild, moderate, and severe renal impairment will further help in guiding better dosing decision for CONTRAVE. Therefore, sponsor could conduct a systematic evaluation of PK of CONTRAVE in subjects with mild, moderate, and severe renal impairment.

3. **In vivo DDI study with OCT2 substrate:** An *in-vitro* drug-drug interaction (DDI) study was conducted by the sponsor to evaluate whether naltrexone, bupropion, and their respective metabolites inhibit Organic Cation Transporter 2 (OCT2), which is involved in the tubular secretion of several drugs and creatinine. The *in-vitro* study results showed that bupropion and its metabolites inhibit OCT2 (Free Cmax/IC50 >0.1 for threohydro- and erythrohydro-bupropion combined), and suggest that clinically relevant interaction through inhibition of OCT2 could occur at therapeutic bupropion doses. Therefore, an *in vivo* evaluation of DDI potential will help in appropriate labeling of CONTRAVE. This evaluation was considered as a PMR during the original NDA submission review. However, newly submitted information from CV safety evaluation revealed that a high proportion of patients were type 2 diabetic and were using metformin doses ranging from 5000 mg to 2000 mg. The data suggests that, from a safety perspective there were very few hypoglycemia adverse reactions seen from this interim data.

   To some extent this information indicates a lack of concern with the co-administration of metformin and CONTRAVE and possibly lack of significant interaction between CONTRAVE and metformin. However, depending upon the capability of metformin to induce hypoglycemia, this information does not completely rules out the DDI concern based on OCT2 inhibition. Therefore, the labeling language is proposed to capture the in vitro potential of CONTRAVE components to inhibit OCT2 and advising caution in concomitant use of OCT2 substrates. Sponsor could conduct a DDI study with a suitable OCT2 substrate, such as metformin, to evaluate the *in vivo* potential of CONTRAVE constituents (bupropion and naltrexone) to inhibit OCT2 and further refine the labeling language based on results of the study.

2. Detailed Labeling Recommendations

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has following labeling recommendations for the revisions to sponsor's proposed language based on the information reviewed under current submission.
[Note: The underlined blue text is the recommended revision and strikethrough (~~abe~~) text is the deletion]

1. Highlights

WARNINGS AND PRECAUTIONS

Risk of seizure may be minimized by adhering to the recommended dosing schedule and avoiding co-administration with high-fat meal. (5.2)

Drug Interactions

- MAOIs: Increased risk of hypertensive reactions can occur when used concomitantly. (b) (4) . (7.1)
- Drugs metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of: (b) (4) antidepressants, (e.g., selective serotonin reuptake inhibitors and many tricyclics), antipsychotics (e.g., haloperidol, risperidone and thioridazine), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., propafenone and flecainide): Consider dose reduction when using with CONTRAVE. (7.3)
- Concomitant treatment with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) can increase bupropion exposure. Avoid concomitant use with CYP2B6 inhibitors. (7.4)
- CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin) may reduce efficacy by reducing bupropion exposure, avoid concomitant use. (7.4)
- Drugs that lower seizure threshold: Dose CONTRAVE with caution. (5.2, 7.5)
- Dopaminergic drugs (levodopa and amantadine): CNS toxicity can occur when used concomitantly with CONTRAVE. (7.7)
- Drug-laboratory test interactions: CONTRAVE can cause false-positive urine test results for amphetamines. (7.8)

Section 2. Dosage and Administration

2.2 Dose Adjustment in Patients With Renal Impairment

No dose adjustment is needed in patients with mild renal impairment. The maximum recommended maintenance dose for CONTRAVE is two tablets per day (one tablet b.i.d, i.e., one tablet each in morning and in evening) in patients with moderate or severe renal impairment. CONTRAVE is not recommended for use in patients with end stage renal disease. [*see Use in Specific Population (8.6) and Clinical Pharmacology (12.3)]*

2.3 Dose Adjustment in Patients With Hepatic Impairment

The maximum recommended dose of CONTRAVE is one tablet per day taken in the morning in patients with hepatic impairment. [*see Use in Specific Population (8.7) and Clinical Pharmacology (12.3)*]

2.4 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Antidepressant

At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with CONTRAVE. Conversely, at least 14 days should be allowed after stopping CONTRAVE before starting an MAOI antidepressant [*see Contraindications (4) and Drug Interactions (7.1)*].

Section 5.2 Under warning and Precautions

Recommendations for Reducing the Risk of Seizure: Clinical experience with bupropion suggests that the risk of seizure may be minimized by adhering to the recommended dosing schedule, in particular:

- the total daily dose of CONTRAVE does not exceed 360 mg bupropion
- the daily dose is administered in divided doses (twice daily)
- the dose is escalated gradually
- no more than two tablets should be taken at one time
- avoid co-administration of CONTRAVE with high-fat meals [*see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)*]

if a dose is missed, a patient should wait until their next scheduled dose and resume the regular dosing schedule.

7. DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors (MAOI)

Concomitant use of MAOIs and bupropion is contraindicated. Bupropion inhibits the reuptake of dopamine and norepinephrine and can increase risk of hypertensive reactions when used concomitantly with drugs that also inhibit the reuptake of dopamine or norepinephrine, including MAOIs. (b) (4) (b) (4) Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAOI phenelzine. At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with CONTRAVE. Conversely, at least 14 days should be allowed after stopping CONTRAVE before starting an MAOI [see *Contraindications (4)*].

7.2 Opioid Analgesics

Patients taking CONTRAVE may not fully benefit from treatment with opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued and opiate dose should not be increased above the standard dose. CONTRAVE may be used with caution after chronic opioid use has been stopped for 7 to 10 days in order to prevent precipitation of withdrawal *[see Contraindications (4)* and *Warnings and Precautions (5.3)]*.

During CONTRAVE clinical studies, the use of concomitant opioid or opioid-like medications, including analgesics or antitussives were excluded.

7.3 Potential for CONTRAVE to Affect Other Drugs (b) (4) (b) (4) **Metabolized by CYP2D6**

In a clinical study, CONTRAVE (32 mg naltrexone/360 mg bupropion) daily was coadministered with a 50 mg dose of metoprolol (a CYP2D6 substrate). CONTRAVE increased metoprolol AUC and C_{max} by approximately 4- and 2-fold, respectively, relative to metoprolol alone. Similar clinical drug interactions resulting in increased pharmacokinetic exposure of CYP2D6 substrates have also been observed with bupropion as a single agent with desipramine or venlafaxine.

Co-administration of [redacted] (b) (4) CONTRAVE with drugs that are metabolized by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclics), antipsychotics (e.g., haloperidol, risperidone and thioridazine), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., propafenone and flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If CONTRAVE 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 *[see Clinical Pharmacology (12.3)]*.

7.4 Potential for Other Drugs to Affect CONTRAVE

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between CONTRAVE and drugs that are inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6: Ticlopidine and Clopidogrel: Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Avoid concomitant use with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) [see Clinical Pharmacology (12.3)].

Inducers of CYP2B6: Ritonavir, Lopinavir, and Efavirenz: Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure and may reduce efficacy. Avoid concomitant use with ritonavir, lopinavir, or efavirenz [see Clinical Pharmacology (12.3)].

Drugs That Lower Seizure Threshold

Use extreme caution when coadministering CONTRAVE with other drugs that lower seizure threshold (e.g, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses and increase the dose gradually [see *Contraindications (4) and Warnings and Precautions (5.2)*].

Dopaminergic Drugs (Levodopa and Amantadine)

Levodopa and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution when administering CONTRAVE concomitantly with these drugs.

7.7 Use With 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 bupropion. The consumption of alcohol during treatment with CONTRAVE should be minimized or avoided.

7.8 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

7.9 Drug-transporter based Interactions

In vitro, *CONTRAVE constituents inhibited the renal organic cation transporter, OCT2 to a clinically relevant level. The systemic concentrations of substrate drugs transported by OCT2 (e.g. Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine,*

metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin) , are likely to increase due to reduced renal clearance when co-administered with CONTRAVE. Co-administration of CONTRAVE with such drugs should be approached with caution and patients need to be monitored for adverse effects.

Section 8 Use in Specific Population

8.6 Renal Impairment

CONTRAVE has not been evaluated in subjects with moderate or severe renal impairment. Based on information available for the individual constituents, systemic exposure is significantly higher for bupropion and metabolites (two to three-fold), and naltrexone and their metabolites in subjects with moderate-to-severe renal impairment. Therefore, the maximum recommended daily maintenance dose for CONTRAVE is two tablets (one tablet each in morning and in evening) in patients with moderate or severe renal impairment. CONTRAVE is not recommended for use in patients with end stage renal disease.*[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

(b) (4)

8.7 Hepatic Impairment

CONTRAVE has not been evaluated in subjects with hepatic impairment. Based on information available for the individual constituents, systemic exposure is significantly higher for bupropion and metabolites (two to three-fold), and naltrexone and their metabolites (up to 10 fold higher) in subjects with moderate-to-severe hepatic impairment. Therefore, the maximum recommended daily dose of CONTRAVE is one tablet in the morning in patients with hepatic impairment.*[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*

(b) (4)

Section 12.3 Pharmacokinetics

(b) (4)

Absorption (b) (4)

Naltrexone

Following single oral administration of CONTRAVE (2 x 8mg Naltrexone/90 mg Bupropion tablet) to healthy subjects, mean peak naltrexone concentrations (Cmax), time

to peak concentration (Tmax), and extent of exposure (AUC0-inf) are 1.3 ng/mL, 2 hr, and 8.2 ng*hr/mL, respectively.

Bupropion

Following single oral administration of CONTRAVE (2 x 8mg Naltrexone/90 mg Bupropion tablet) to healthy subjects, mean peak bupropion concentrations (Cmax), time to peak concentration (Tmax), and extent of exposure (AUC0-inf) are 166 ng/mL, 3 hr, and 1574 ng*hr/mL, respectively.

(b) (4)

[redacted]

Food Effect on Absorption

When CONTRAVE was given with a high-fat meal the AUC and C_{max} for naltrexone increased 2.1-fold and 3.7-fold and the AUC and C_{max} for bupropion increased 1.4-fold and 1.8-fold, respectively. At steady state, the food effect resulted in AUC and C_{max} increases of 1.7- and 1.9-fold for naltrexone, and 1.1- and 1.3-fold for bupropion, respectively. Thus, CONTRAVE should not be taken with high-fat meals due to the significant increases in bupropion and naltrexone systemic exposure in the presence of a high-fat meal.

Distribution

Naltrexone

Naltrexone is 21% plasma protein bound. The mean apparent volume of distribution at steady state for naltrexone, V_{ss}/F, was 5697 liters.

Bupropion

Bupropion is 84% plasma protein bound. The mean apparent volume of distribution at steady state for bupropion, V_{ss}/F, was 880 liters.

(b) (4)

Metabolism and Excretion

(b) (4)

Naltrexone

The major metabolite of naltrexone is 6-beta-naltrexol. The activity of naltrexone is believed to be due to both parent and the 6-beta-naltrexol metabolite. Though less potent, 6-beta-naltrexol is eliminated more slowly and thus circulates at much higher concentrations than naltrexone. Naltrexone and 6-beta-naltrexol are not metabolized by cytochrome P450 enzymes and *in vitro* studies indicate that there is no potential for inhibition or induction of important isozymes.

Naltrexone and its metabolites are excreted primarily by the kidney (53% to 79% of the dose). Urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose. Urinary excretion of unchanged and conjugated 6-beta-naltrexol accounts for 43% of an oral dose. The renal clearance for naltrexone ranges from 30 to 127 mL/min suggesting that renal elimination is primarily by glomerular filtration. The renal clearance for 6-beta-naltrexol ranges from 230 to 369 mL/min suggesting an additional renal tubular secretory mechanism. Fecal excretion is a minor elimination pathway.

Following single oral administration of CONTRAVE tablets to healthy subjects, mean elimination half-life ($T_{½}$) was approximately 5 hours for naltrexone. Following twice daily administration of CONTRAVE, naltrexone does not accumulate and its kinetics appears linear. However, in comparison to naltrexone, 6-beta-naltrexol accumulates to a larger extent (accumulation ratio ~3).

Bupropion

Bupropion is extensively metabolized with three active metabolites: hydroxybupropion, threohydrobupropion and erythrohydrobupropion. The metabolites have longer elimination half-lives than bupropion and accumulate to a greater extent. Following bupropion administration >90% of the exposure is due to metabolites. *In vitro* findings suggest that CYP2B6 is the principal isozyme involved in the formation of hydroxybupropion while cytochrome P450 isozymes are not involved in formation of the other active metabolites. Bupropion and its metabolites inhibit CYP2D6. Plasma protein binding of hydroxybupropion is similar to that of bupropion (84%) whereas the other two metabolites have approximately half the binding.

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. The fraction of

the oral dose of bupropion excreted unchanged was 0.5%, a finding consistent with the extensive metabolism of bupropion.

Following single oral administration of CONTRAVE tablets to healthy subjects, mean elimination half-life ($T_{½}$) was approximately 21 hours for bupropion. Following twice daily administration of CONTRAVE, metabolites of bupropion, and to a lesser extent unchanged bupropion, accumulate and reach steady state concentrations in approximately one week.

(b) (4)-Specific Populations

Gender

Pooled analysis of CONTRAVE data revealed no clinically meaningful (b) (4) differences in the pharmacokinetic parameters of bupropion or naltrexone. (b) (4)

Race

Pooled analysis of CONTRAVE data revealed no clinically meaningful differences in the pharmacokinetic parameters of bupropion or naltrexone based on race. (b) (4)

Hepatic Impairment

Pharmacokinetic data are not available with CONTRAVE in patients with hepatic impairment. The following information is available for individual constituents: (b) (4)

Naltrexone

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.

Bupropion

Renal Impairment

(b) (4) Following information is available for the individual constituents:

Naltrexone

Limited information is available for naltrexone in patients with moderate to severe renal impairment. In a study of seven patients with end-stage renal disease requiring dialysis, peak plasma concentrations of naltrexone were elevated (b) (4) fold compared to healthy subjects.

Bupropion

Limited information is available for (b) (4) bupropion……Dose of CONTRAVE should be reduced in patients with moderate and severe renal impairment. CONTRAVE is not recommended for use in patients with end stage renal disease*[see Dosage and Administration* (2,3) and *Use in Specific Populations (8.6)]*.

Drug Interactions

In vitro Assessment of Drug Interactions

At therapeutically relevant concentrations, naltrexone or 6-beta-naltrexol are not a major inhibitor of CYP isoforms: CYP1A2, CYP2B6, CYP2C8, CYP2E1 CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Both naltrexone and 6β-naltrexol are not major inducers of CYP isoforms: CYP1A2, CYP2B6, or CYP3A4.

In vitro, bupropion (IC50=9.3 µM) and its metabolites: hydroxybupropion (IC50=82 µM), threohydrobupropion and erythrohydrobupropion (1:1 mixture; IC50=7.8 µM) inhibited the renal organic cation transporter, OCT2 to a clinically relevant level. The systemic concentrations of substrate drugs transported by OCT2 are likely to increase due to reduced renal clearance when co-administered with CONTRAVE.

We recommend that sponsor should present the following highlighted label text in a tabular format for describing DDIs:

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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/s/

MANOJ KHURANA
05/23/2014

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ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**200-063/S-000 resubmission**
Submission Date:	12/10/2013
Drug Name:	Contrave (naltrexone HCl bupropion HCl)
Formulation:	ER Tablets
Strength:	4/90 and 8/90 mg (naltrexone HCl/bupropion HCl)
Applicant:	Orexigen
Reviewer:	John Duan, Ph.D.
Submission Type:	NDA resubmission

BACKGROUND

NDA 200-063 for CONTRAVE is proposed for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, to be used in conjunction with lifestyle modification. The current submission is to address the deficiency noted in the Complete Response Letter issued on 1/31/2011. This review will focus on the issue regarding dissolution specifications.

COMMENTS

The Applicant's responses regarding the dissolution specifications and the in vitro alcohol dose dumping study are acceptable.

RECOMMENDATION

ONDQA-Biopharmaceutics Team has reviewed the resubmission of NDA 200-063 for CONTRAVE and found it is acceptable. An approval is recommended from the Biopharmaceutics perspective.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Tapash Ghosh, Ph.D. Date
Team Leader
ONDQA Biopharmaceutics

cc: NDA 200-063 *DARRTS, RLostritto*

BIOPHARMACEUTICS EVALUATION

1. Introduction

NDA 200-063 for CONTRAVE is proposed for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, to be used in conjunction with lifestyle modification. The proposed commercial drug product will be manufactured (under contract) by (b) (4) located in (b) (4) It is formulated as an extended release trilayer tablet containing two active ingredients: bupropion hydrochloride in one layer, an inert middle layer, and naltrexone hydrochloride in the other layer. The drug product manufacturing process consists of (b) (4) There are two drug product strengths, both with a single strength (90 mg) of bupropion hydrochloride per tablet, one with 4 mg naltrexone hydrochloride per tablet, and the other with 8 mg naltrexone hydrochloride per tablet. The tablets are film coated, using (b) (4) Opadry® II Blue (for the 8 mg naltrexone hydrochloride/ tablet product).

The original submission was dated on 3/31/2010. A complete response letter (CRL) was issued on 1/31/2011. The current submission is to address the deficiency noted in the CRL.

2. Drug Product Unit Composition:

The composition of Naltrexone Hydrochloride/Bupropion Hydrochloride (4 mg/90 mg) is shown in the following table.

(b) (4)

The composition of Naltrexone Hydrochloride/Bupropion Hydrochloride (8 mg/90 mg) is shown in the following table.

Ingredient	Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet[1]	
(b) (4)				
Bupropion Hydrochloride USP	90.0		(b) (4)	Active ingredient
L-Cysteine Hydrochloride USP	(b) (4)			(b) (4)
Microcrystalline Cellulose (b) (4) NF				
Hydroxypropyl Cellulose (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
Microcrystalline Cellulose (PH-101) NF				
Lactose Anhydrous NF				
Crospovidone (b) (4) NF				
Magnesium Stearate NF				
FD&C Blue #2 Aluminum Lake				
(b) (4)				
Naltrexone Hydrochloride (b) (4) USP	8.0			Active ingredient
Microcrystalline Cellulose (b) (4) NF	(b) (4			(b) (4)
Hypromellose USP (b) (4)				
Hydroxypropyl Cellulose (b) (4) NF				
Edetate Disodium USP				
Colloidal Silicon Dioxide NF				
Lactose Monohydrate (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
				(b) (4)
(b) (4)				
Opadry II				
Overall total:	680		100	

3. Response to deficiency regarding dissolution specifications

The Agency proposed a revised dissolution specification for naltrexone/bupropion in the January 31, 2011 Complete Response Letter (CRL) as follows.

> **Based on the information provided, your choice of dissolution method is acceptable. However, your proposed dissolution specifications are not acceptable. Based on the dissolution results from the stability batches, the following table describes our recommendation for your proposed 8 mg/90 mg naltrexone hydrochloride and bupropion hydrochloride product with a side-by-side comparison to your proposed specifications:**

Actives	Time (Hr)					
	0.5	1	2	3	4	6
Sponsor's Proposed Specifications						
Naltrexone HCl	(b) (4)					
Bupropion HCl						
Agency's Recommended Specifications						
Naltrexone HCl	(b) (4)					
Bupropion HCl						

Apparatus:	2 (Paddles)
Dissolution Media:	Water (degassed)
Media Volume:	900 mL
Temperature:	37 ± 0.5 °C
Shaft Speed:	50 RPM
Sampling Interval:	30 minutes, 1, 2, 3, 4, 6 hours
Sample Volume:	10 mL

The Applicant evaluated the in vitro dissolution data of naltrexone using comprehensive statistical analysis of relevant clinical Phase 3 and Phase 1 (bioavailability) lots, including the [redacted] lots manufactured [redacted] to support ongoing clinical trials. A further refined specification was proposed. A summary of the Agency's recommendation and the Applicant's revised proposal is provided below.

Active Ingredient	Time (h)					
	0.5	1	2	3	4	6
Agency's Recommended Specification in the CRL						
Naltrexone HCl	[redacted]%	[redacted]%	[redacted]%	NLT [redacted]%	---	---
Sponsor's *Revised* Proposed Specification						
Naltrexone HCl	[redacted]%	[redacted]%	---	---	NLT [redacted]%	---

Based on statistical analysis of the relevant batches from [redacted] clinical batches manufactured to date (table below), the proposed specification range was selected as [redacted]% of the overall batch mean for 0.5 h and 1 h time points, and in consideration of individual tablet variability at the early time points. According to the Applicant, the selection of a [redacted]% range for the 0.5 hour time point does not pose a safety risk given that the naltrexone Cmax is less than [redacted]% of that observed with approved naltrexone immediate-release (IR) tablet formulations.

A 1 hour middle time point with a specification range of [redacted]% was recommended by the Agency in the complete response letter and during the Type C meeting between Orexigen and Agency on 24 October 2013. Due to within batch variability for the early time points, a specification of [redacted]% would lead to three of the pivotal clinical lots failing this specification. Therefore, a range of [redacted]% is proposed, which better describes the performance of pivotal clinical batches. This range is not centered on the 1 hour mean value due to the individual high results observed in the clinical lot data set.

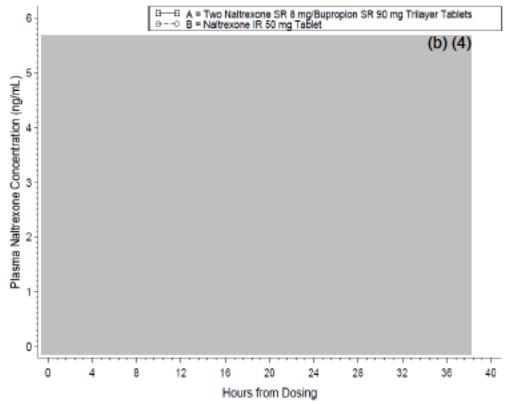
The Agency recommended NLT [redacted]% at a 3 hour time point in the Complete Response Letter (CRL). A 3 hour time point was evaluated in response to the Agency suggestion, and the analysis showed that several clinical lots would not meet this acceptance criterion as shown in the statistical data in the following table. Based on the statistical analysis of release and stability data from clinical and registration batches, a time point of 4 hours with NLT [redacted]% provides more reliable assurance that the drug product release of naltrexone is complete, and this time point allows use of the more stringent NLT [redacted]% acceptance criterion recommended by the Agency without undue risk of batch failure.

Time Point	Population Mean	Min (Mean*)	Max (Mean*)	Population Mean SD	Individual Pooled SD
Naltrexone 0.5 h	37.5	33.0	43.3	2.4	[redacted]
Naltrexone 1 h	57.7	51.0	65.8	3.5	
Naltrexone 3 h	89.8	83.8	98.8	2.4	
Naltrexone 4 h	93.6	86.5	102.0	2.5	

* mean result from release and stability at 25 C/60%RH

The [redacted] of in vitro naltrexone release observed at the early (0.5 hour) and middle (1 hour) time points indicates the need to apply a [redacted]%) at those time points. In evaluating the validity of applying a [redacted]% range for the 0.5 hour and 1 hour time points for naltrexone, the Applicant has taken into consideration the attributes of naltrexone/bupropion in vivo product performance to justify the proposed specifications:

A (b) (4)% range at the 0.5 hour time point is supported given the relatively low systemic exposure of naltrexone observed with the extended-release formulation and subsequently minimal clinical concern associated with dose dumping. This is based on results of a comparative relative bioavailability study demonstrating that mean Cmax and AUC of naltrexone following administration of two naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets are (b) (4), respectively, than those of FDA approved naltrexone 50 mg IR tablets (Study NB-230) as shown in the following figure.



Naltrexone is known to be associated with high intrinsic PK variability as evidenced by published studies as well as the results of Study NB-230, which compared the bioavailability of the NB trilayer sustained release tablet to a marketed immediate release naltrexone tablet. High variability (% CV (b) (4)%) in mean Cmax estimate was observed in the study with both the marketed immediate release naltrexone tablet and the trilayer (b) (4) tablet, showing that the observed high PK variability is an inherent property of naltrexone drug substance and is not related to the trilayer tablet product release characteristics as listed in the following table.

Mean (SD)	Formulation (Dose) Source		
	NB (8 mg/90 mg) Study NB-230	Naltrexone IR (50 mg) Study NB-230	Naltrexone IR (50 mg) Meyer et al. 1984
N	26	24	24
Cmax	1.36 (0.91)	7.55 (4.62)	8.55 (4.84)
AUC0-∞ (ng•h/mL)	8.40 (4.57)	27.25 (12.60)	24.82 (14.56)

Based on the Applicant, small changes in the timing and extent of naltrexone release in vivo are unlikely to meaningfully alter the pharmacodynamic response (mu-opioid receptor occupancy). This is demonstrated by the results of a receptor occupancy study (IR-PET) that indicated at the 1 hour time point an adequate degree of occupancy by naltrexone (estimated to be (b) (4) over a three-fold range of doses bracketing the intended commercial dose of two NB 8/90 tablets administered twice daily as shown in the following table.

Naltrexone Dose (mg)	NB 8/90 Tablet Equivalents	Receptor Binding at 1 Hour After Dosing		
		Mean	SD	90% CI
8	1	74.63	4.03	72.13, 77.13
16	2	88.37	4.30	85.71, 91.03
32	4	87.59	3.68	85.31, 89.88

The Applicant also argues that small differences in the rate of tablet dissolution are not expected to alter the efficacy or result in meaningful differences in the safety profile. Long-term efficacy and safety have been observed across a two-fold range of naltrexone doses. Total daily NB doses of 16/360 (NB16, a lower dose not intended for commercialization) and 32/360 (NB32, the intended commercial dose) were studied in one of the one-year Phase 3 studies (NB-301). While weight loss observed with NB32 exceeded that observed with NB16, both doses exhibit acceptable degrees of weight loss as shown in the following table.

	Treatment		
	Placebo	**NB16 (Two NB 4/90 Tablets BID)**	**NB32 (Two NB 8/90 Tablets BID)**
N	511	471	471
Mean Baseline Body Weight (kg)	99.29	100.11	100.17
Mean % Change from Baseline to Endpoint	-1.27	-4.94	-6.07
Proportion of Subjects Achieving ≥5% Weight Loss at Endpoint	16.44%	39.49%	47.98%

The tolerability profiles are shown in the following table (similar between the two doses).

	Incidence (% of Subjects)		
Preferred Term	**Placebo (N=569)**	**NB16 (N=569)**	**NB32 (N=573)**
Nausea	5.3	27.2	29.8
Constipation	5.6	15.8	15.7
Vomiting	2.5	6.3	9.8
Dry Mouth	1.9	7.4	7.5
Diarrhoea	4.9	5.4	4.5

In addition, the Applicant states that due to accumulation of the active naltrexone metabolite 6β-naltrexol with chronic dosing and long duration of binding of naltrexone to the mu-opioid receptor, small differences in the timing of naltrexone release in the in vitro setting are unlikely to meaningfully impact overall in vivo systemic exposure to the pharmacologically active moieties (i.e., parent compounds and their metabolites). The extent of accumulation of the pharmacologically active metabolite 6β-naltrexol that occurs over time needs to be considered when developing in vitro dissolution specifications. While the degree of accumulation of naltrexone at steady-state is relatively minor (~7%), there is significant accumulation of 6β-naltrexol due to a long terminal elimination half-life as shown in the flowing table. Given this accumulation, in addition to the observation that the half-life of naltrexone receptor occupancy is greater than 100 hours, small differences in the timing of naltrexone release in the in vitro setting are unlikely to meaningfully impact overall in vivo systemic exposure to the pharmacologically active moieties.

Plasma 6β-naltrexol	
$AUC_{ratio,M-P}$	44.56 ± 20.91
$Cmax_{ratio\ M-P}$	24.47 ± 10.15

In light of these findings and considerations, the Applicant deems that the proposed naltrexone dissolution specifications are adequate.

For Bupropion hydrochloride dissolution specifications, the Applicant has evaluated the Agency-proposed changes to the product in vitro dissolution specifications employing comprehensive statistical analysis of relevant clinical Phase 3 and Phase 1 (bioavailability) lots, including the (b) (4) lots manufactured since (b) (4) to support ongoing trials, and believes that a further refined specification would more appropriately support product characteristics and performance

while adhering to regulatory guidance. A summary of the Agency's recommendation and the sponsor's revised proposed specification is provided below.

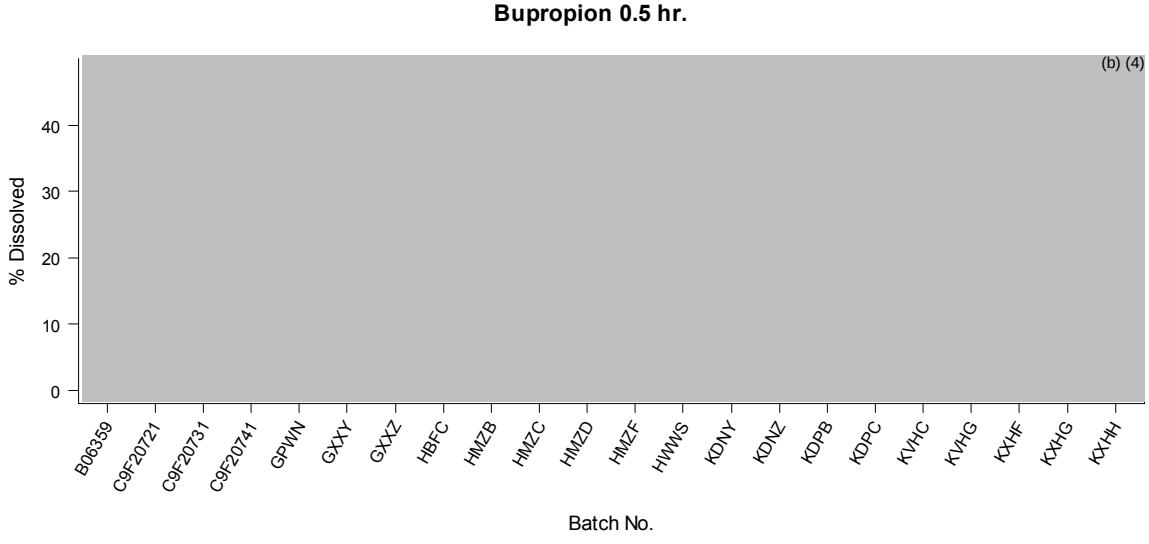
Active Ingredient	Time (h) 0.5	1	2	3	4	6
Agency's Recommended Specification in the CRL						
Bupropion HCl	(b) (4)					---
Sponsor's *Revised* Proposed Specification						
Bupropion HCl	(b) (4)					

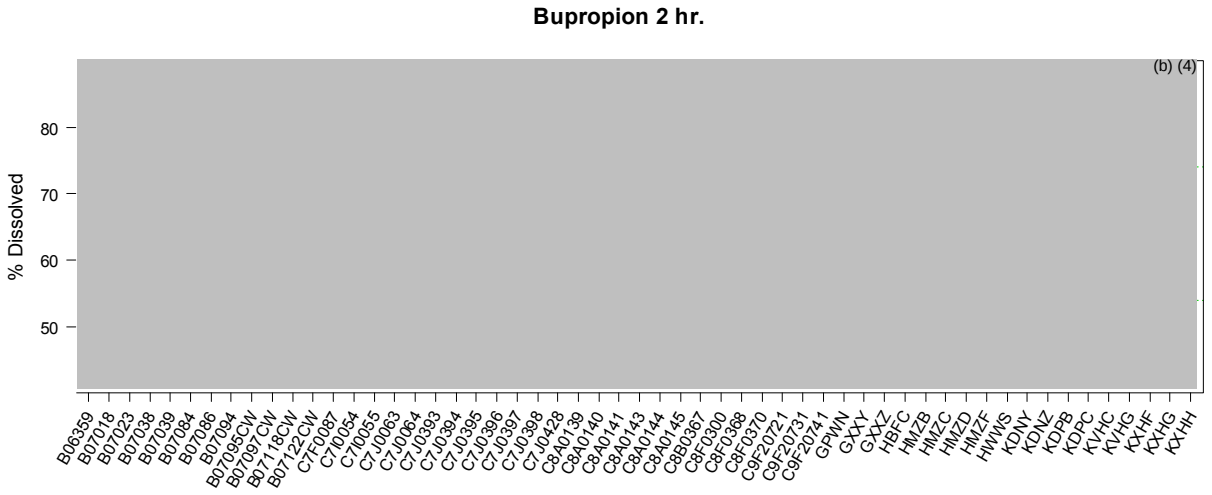
The proposal is based on a statistical analysis of the overall batch mean from (b) (4) clinical batches manufactured to date as shown in the following table. These specification ranges are in line with that proposed by the Agency in the CRL. The last time point of 6 hours was selected to ensure at least (b) (4)% of drug has dissolved. The Agency proposed NLT (b) (4)% at the 4 hour time point in CRL. However, more data have been generated since the original submission, and based on the statistical analysis and specification for bupropion drug content ((b) (4)% of claimed amounts throughout product life), an end-of-release time point of 6 hours with NLT (b) (4)% provides assurance that bupropion has achieved near complete release (at or above (b) (4)%).

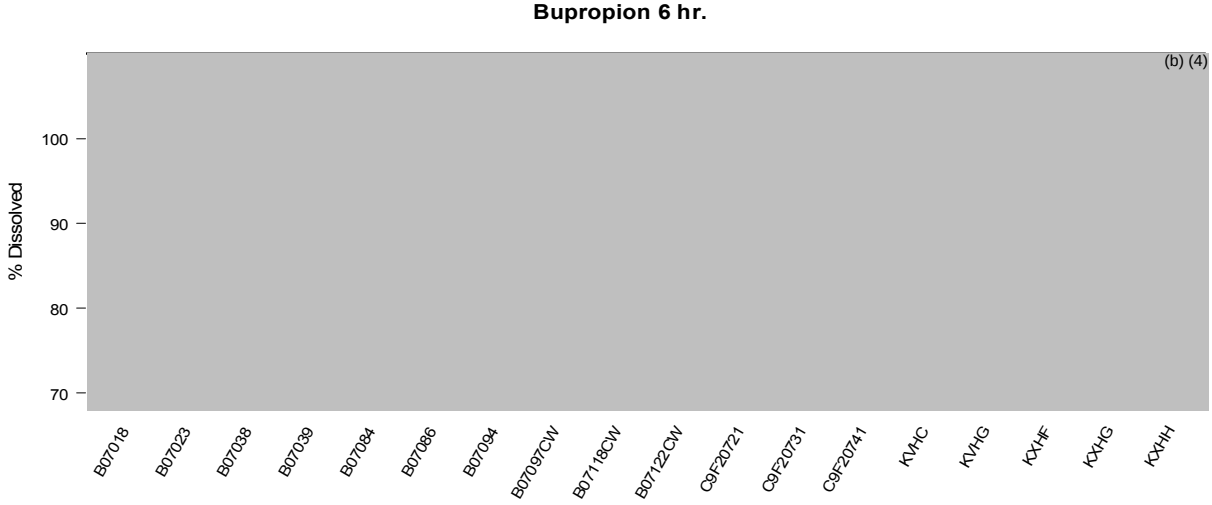
Time Point	Population Mean	Min (Mean*)	Max (Mean*)	Population Mean SD	Individual Pooled SD
Bupropion 0.5 h	24.5	22.9	28.6	0.8	(b) (4)
Bupropion 2 h	64.0	58.3	69.6	3.0	
Bupropion 4 h	87.1	80.8	92.7	2.8	
Bupropion 6 h	95.4	93.5	98.8	1.1	

Reviewer's Comments: *The responses are acceptable.*

1. *The proposed acceptance criteria at 0.5, 2 and 6 h for bupropion are in line with the Agency's recommendations. The following figures show the dissolution data overlapped with the proposed acceptance criteria.*





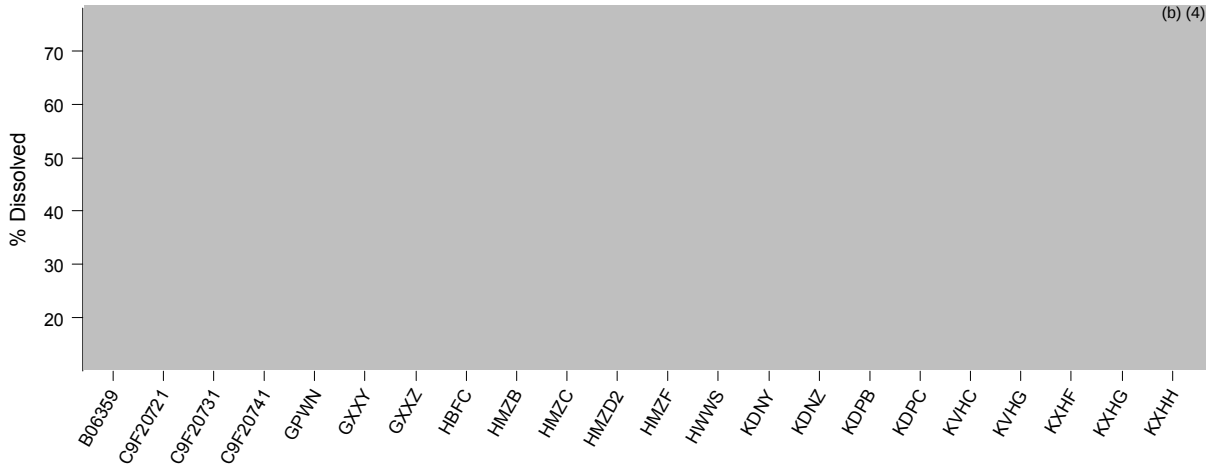


2. *The Applicant's arguments using in vivo PK and PD of naltrexone to justify its in vitro dissolution specifications are reasonable based on the following considerations.*

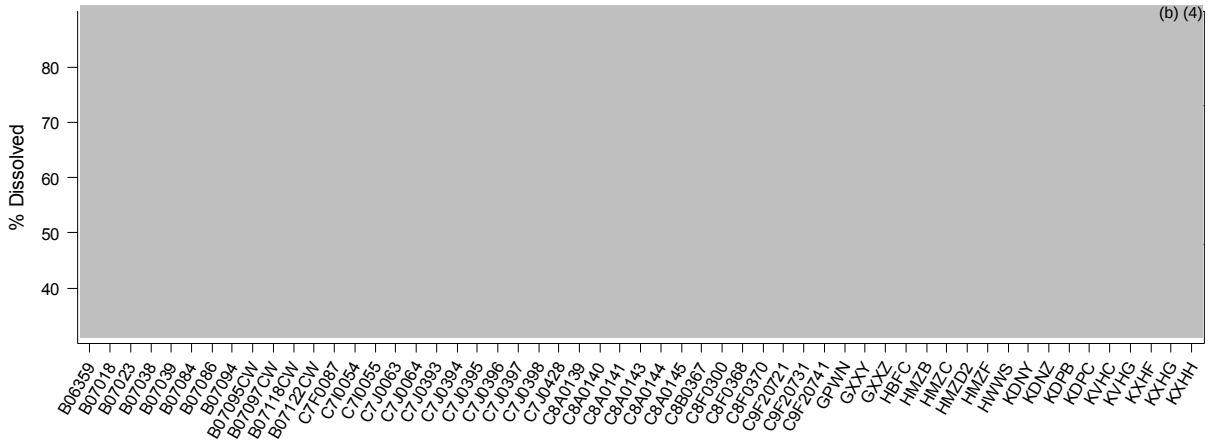
    a. *The high intrinsic PK variability is evidenced by the study results provided.*
    b. *The mu-opioid receptor occupancy study showed an adequate degree of occupancy by naltrexone at 1 hour time point and therefore the small changes in the timing and extent of release in vivo may not alter the PD response.*
    c. *Due to accumulation of the active naltrexone metabolite 6β-naltrexol with chronic dosing and long duration of binding of naltrexone to the mu-opioid receptor, small differences in the timing of naltrexone release in the in vitro setting are unlikely to meaningfully impact overall in vivo systemic exposure to the pharmacologically active moieties*

3. *The release and stability data support the proposed specification for naltrexone as shown in the following figures.*

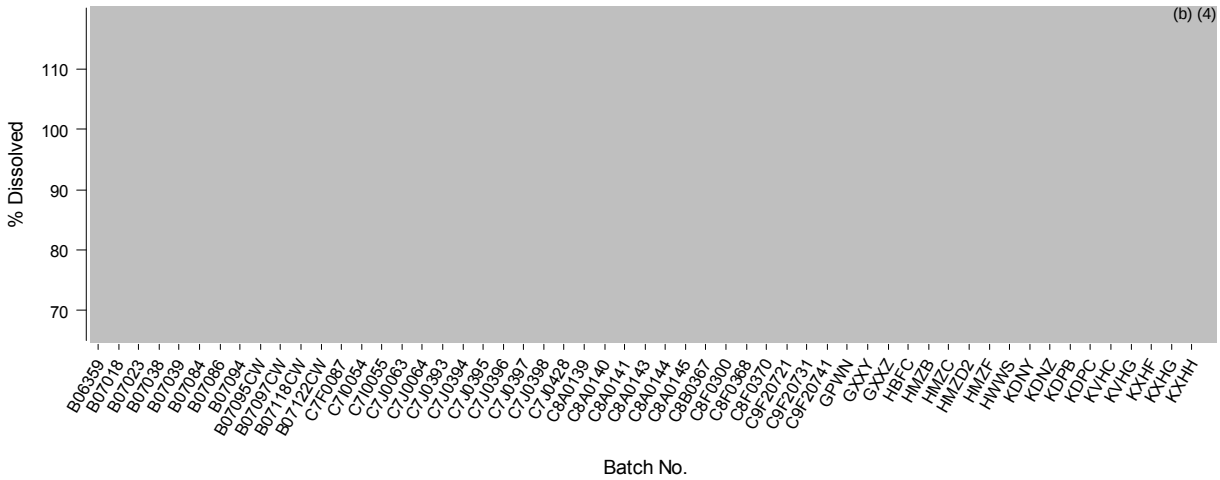
Naltrexone 0.5 hr.



Naltrexone 1 hr.



Naltrexone 4 hr.



4. Response to comments regarding in vitro alcohol dose dumping study.

The Agency made comments on the evaluation of the alcohol induced dose dumping in the 31 January 2011 Complete Response Letter (CRL) as follows.

Your evaluation of the effect of alcohol (ethanol) on the in-vitro dissolution of bupropion hydrochloride or naltrexone hydrochloride, as submitted in this application, is deficient. You did not investigate testing in 0.1 N HCl (pH 1.2) containing a range of alcohol concentrations to evaluate potential for in-vivo dose dumping in presence of ethanol. Provide these data as soon as they are available.

In response to recommendations in the FDA's Complete Response Letter, studies were performed to address the possibility of dose dumping of bupropion hydrochloride and naltrexone hydrochloride when the extended release drug product is taken with alcohol. Dissolution testing using 0, 5, 20 and 40% ethanol in 0.1 N HCl (pH 1.2) dissolution media was performed. Drug product batch 0890-09034 (b) (4) batch C9F2072) was used for this study, with bupropion hydrochloride and naltrexone hydrochloride data from twelve units in each dissolution run collected every 15 minutes for two hours. The test conditions consist of 900 mL 0.1N HCl, USP Apparatus 1 (baskets) at 75 rpm. The results shown in the following figures (left for bupropion and right for naltrexone) demonstrate that the amounts of bupropion and naltrexone dissolved in the presence of alcohol are reduced suggesting no dose dumping potential.

Reviewer's Comments: *The responses are acceptable. The data for evaluation of the potential alcohol induced dose dumping in 0.1 N HCl were submitted to the background material for the meeting held on 10/24/2013, which were deemed adequate as the meeting minutes state: "We acknowledge the data from the in vitro alcohol interaction study that you submitted in this meeting package. Based on these data, we agree that your proposed product does not demonstrate dose dumping in the presence of alcohol."*

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

/s/

JOHN Z DUAN
05/05/2014

TAPASH K GHOSH
05/05/2014

CLINICAL PHARMACOLOGY REVIEW

NDA: 200063	Submission Date(s): 03/31/2010
Brand Name	CONTRAVE®
Generic Name	Naltrexone Hydrochloride and Bupropion Hydrochloride in combination
Clinical Pharmacology Reviewer	Manoj Khurana, Ph.D.
Clinical Pharmacology Team Leader	Sally Choe, Ph.D.
Primary Pharmacometrics Reviewer	Manoj Khurana, Ph.D.
Secondary Pharmacometrics Reviewer	Christine Garnett, Ph.D.
Pharmacometrics Team Leader	Christine Garnett, Ph.D.
Primary Pharmacogenomics Reviewer	Michael Pacanowski, Pharm.D., M.P.H.
OCP Division Director	Chandrahas Sahajwalla, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Orexigen Therapeutics
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Sustained-release trilayer tablets for oral administration, Naltrexone/Bupropion 4/90 mg and 8/90 mg
Proposed Indication	Treatment of obesity and weight management, including weight loss and maintenance of weight loss, to be used in conjunction with lifestyle modification.

(This part of the Clinical Pharmacology review contains the individual study reviews)

Orexigen Therapeutics (the Sponsor) is seeking an approval of CONTRAVE® (hereafter Contrave or NB) (b) (4) Tablets for the treatment of obesity and weight management. Contrave is a fixed-dose combination drug product containing two active pharmaceutical ingredients, naltrexone hydrochloride (hereafter naltrexone or N**)** and bupropion hydrochloride **(**hereafter bupropion or B). Naltrexone is a μ (mu) opioid antagonist, and bupropion is a dopamine (DA) and norepinephrine (NE) reuptake inhibitor.

Since both active ingredients are approved in the US for use in other indications, this application is submitted by the sponsor as a 505(b)(2) NDA. The sponsor has referenced pertinent information from approved US prescribing information for ReVia® (naltrexone hydrochloride; NDA 18-932) and Wellbutrin SR® (bupropion hydrochloride; NDA 20-358).

Each Contrave tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and claimed to be a (b) (4) tablet. A rapidly dissolving inert layer separates the two drug layers. Contrave will be available as two naltrexone dosage strength tablets:

- CONTRAVE® 8/90, (naltrexone HCL 8 mg/bupropion HCL 90 mg) tablets (hereafter **NB 8/90 mg**)
- CONTRAVE® 4/90, (naltrexone HCL 4 mg/bupropion HCL 90 mg) tablets (hereafter **NB 4/90 mg**)

The individual study reviews are provided in this Part 2 of the OCP review. For the OCP Question Based Review, Pharmacometrics, and Pharmacogenomics Reviews refer to Part 1 of the NDA review: (N200063 QBR_P1_Finalv).

1.1 Individual Study Reviews

1.1.1 PK (NB-230)

Contrave is a combination of naltrexone and bupropion, containing 4 or 8 mg naltrexone and 90 mg bupropion in a sustained release trilayer tablet. The total daily dose is 32 mg (lower than 50 mg naltrexone IR) and 360 mg (higher than the 150 mg bupropion SR), respectively, for naltrexone and bupropion. This study was conducted to answer the question: "How do the PK profile of these two components from intended commercial formulation of Contrave (2 x NB 8/90 mg) compare to the commercially available tablet formulations of naltrexone IR (50 mg) and bupropion SR (150 mg), in healthy adult subjects?".

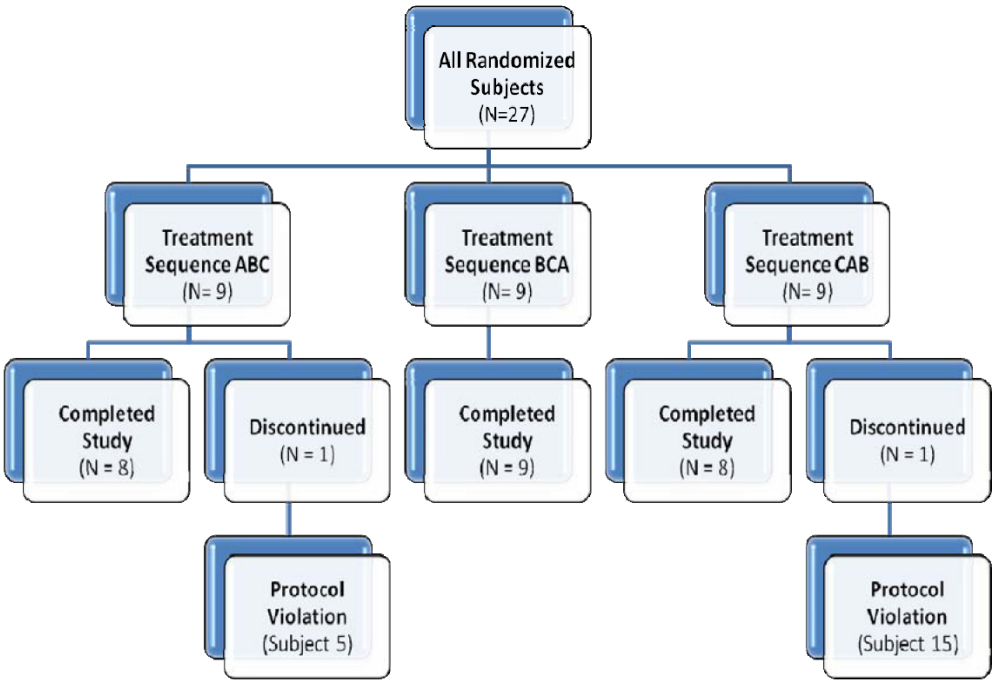
The study design is as follows:

Title:	A Phase 1, Open-Label, Randomized, Single-Dose, Three-Way Crossover Study to Assess the Relative Bioavailability of Naltrexone SR/Bupropion SR Combination Trilayer Tablets to Commercially Available Tablet Formulations of Naltrexone IR and Bupropion SR in Healthy Adult Subjects
Objectives:	**Primary:** To assess the single dose relative bioavailability of naltrexone SR/bupropion SR combination trilayer tablets to commercially available tablet formulations of naltrexone IR and bupropion SR in healthy adult subjects. **Secondary:** To assess the safety and tolerability of the 3 evaluated treatments.
Study Design	The 3 study treatments (A, B, and C) were as follows: A = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Test) B = One Naltrexone IR 50 mg Tablet (Reference 1) C = One Bupropion SR 150 mg Tablet (Reference 2) Prior to the start of the study, each subject was randomly assigned to 1 of 3 treatment sequences according to a Latin square design. The treatment sequence for each subject included all 3 treatments: Treatment A (Test), Treatment B (Reference 1), and Treatment C (Reference 2). Following a fast of at least 10 hours, subjects received a single oral dose of study drug on Day 1 of each treatment period, with a minimum 14-day washout period between dosing days.
Study Population	N= 27 Healthy subjects, Gender: 13 M and 14F, Age: 33 (19-60) yr Weight: 87.5 (53-135) kg, BMI: 30.1 (20-40)
Test Product	The test product was 2 naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets (Treatment A, Test), Lot number C8B0367, manufactured by (b) (4) given as a single oral dose with 240 mL of water.
Reference Products	Naltrexone reference treatment was 1 naltrexone IR 50 mg tablet, (Treatment B, Reference 1), Lot number 307101, manufactured by (b) (4) given as a single oral dose with 240 mL of water;

	Bupropion reference treatment was 1 bupropion SR 150 mg tablet, (Treatment C, Reference 2), Lot number ML080653, manufactured by (b) (4) given as a single oral dose with 240 mL of water.
Sampling: Blood	Blood samples for determination of naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (0 hour), and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 120 hours post-dose. Naltrexone elimination half-life (t1/2) is approximately 4 h, bupropion has a t1/2 of 21 hr; thus, a 120-h plasma concentration versus time profiling appears to be adequate for all analytes.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞,Cmax, Tmax, Kel, t1/2
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Protocol Deviations: There were no protocol deviations with respect to study entry criteria, no subjects who developed withdrawal criteria and were not withdrawn, and no subjects who received the wrong treatment or incorrect dose.

Subject Disposition and Data Sets Analyzed:

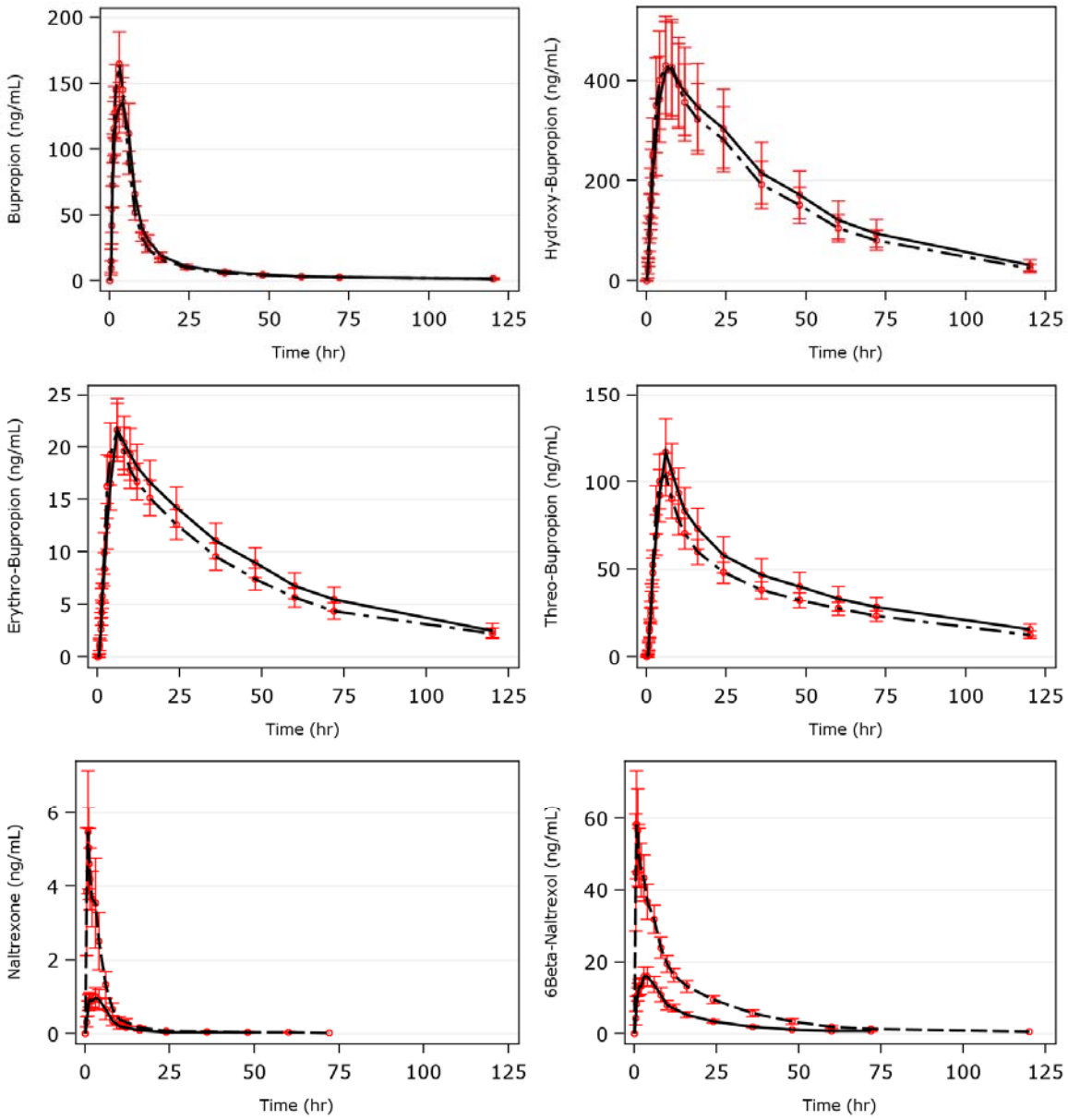


All 27 subjects who were enrolled in the study also received at least 1 formulation and were included in the PK analysis data sets. However, data from 7 of the 27 subjects were either not collected or excluded from certain individual treatment PK summary statistics

and/or statistical analysis for the following reasons; two subjects discontinued from study prior to getting their intended treatment, vomiting occurred at or before 2 times median Tmax in two subjects, unreliable t1/2 estimation in two subjects (AUC0-inf for threohydro/erythrohydro only).

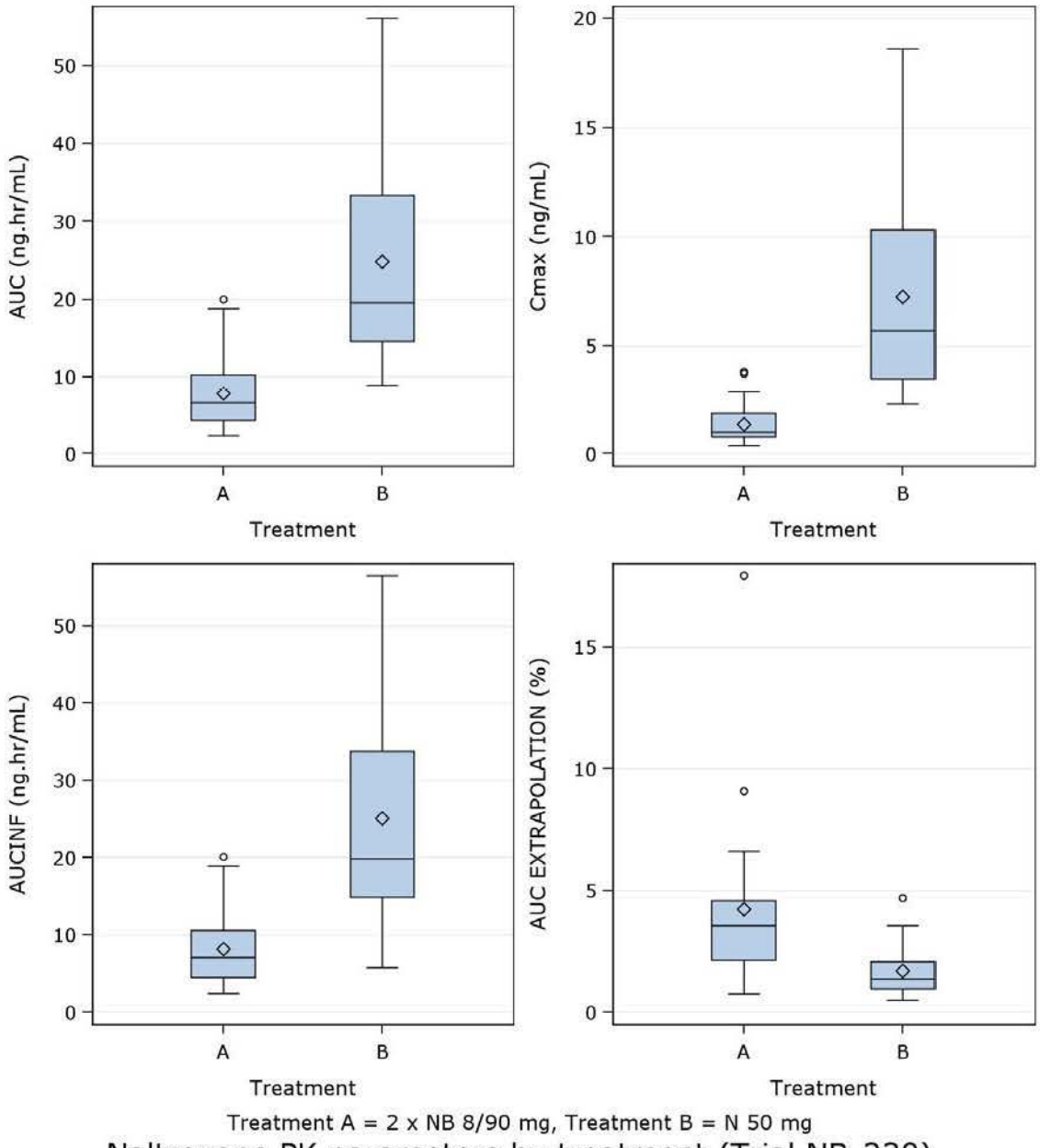
Pharmacokinetic Results:

The concentration-time profiles of all analytes by treatment are shown in Figure below:

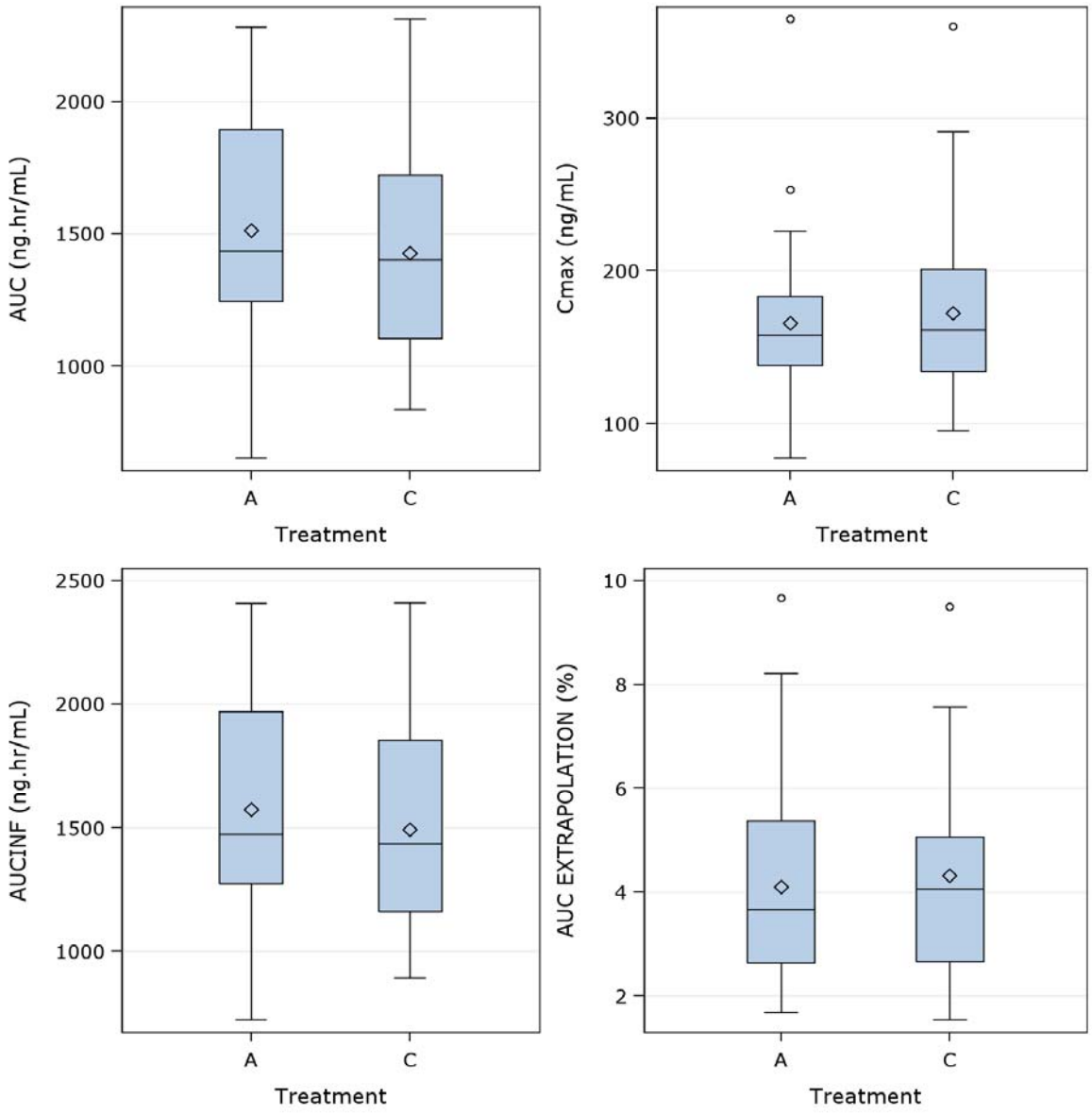


Bupropion and Metabolites:(-)NB8/90, (--) B150
Naltrexone and Metabolite:(-)NB8/90, (--) N50
Mean(±)SE Concentration-time plots by treatment (Trial NB-230)

The distribution of PK parameters by treatment for naltrexone and bupropion is summarized in the figures below:



Naltrexone PK parameters by treatment (Trial NB-230)



Treatment A = 2 x NB 8/90 mg, Treatment C = B 150 mg

Bupropion PK parameters by treatment (Trial NB-230)

The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both naltrexone and bupropion.

The geometric mean ratios and 90% CIs from the statistical comparison of PK parameters are presented in the following tables.

Table 1 Statistical comparison for naltrexone PK parameter

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A-2NB8/90	B-N50	AUC(0-inf)	ng.hr/mL	30.74	26.17 - 36.11
		AUC(0-t)	ng.hr/mL	33.22	27.85 - 39.62
		Cmax	ng/mL	18.71	14.76 - 23.72

Table 2 Statistical comparison for bupropion PK parameter

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A-2NB8/90	C-B150	AUC(0-inf)	ng.hr/mL	103.99	93.43 - 115.75
		AUC(0-t)	ng.hr/mL	103.88	93.69 - 115.18
		Cmax	ng/mL	96.08	85.81 - 107.57

Predicted Naltrexone and Bupropion and Metabolite Pharmacokinetic Parameters (Using Superposition): Naltrexone SR/Bupropion SR q12h Versus Naltrexone IR q24 h and Bupropion SR q12h, respectively:

Analyte	Pharmacokinetic Parameter	N	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Interval
			Nal SR/Bup SR q12h	Nal IR q24h		
Naltrexone	$C_{max,ss}$ (ng/mL)	27	1.276	6.220	20.50	16.62 – 25.30
	AUC_{0-24} (ng*hr/mL)	27	14.473	24.030	60.23	54.65 – 66.38
6-Beta Naltrexol	$C_{max,ss}$ (ng/mL)	27	30.356	87.059	34.87	30.66 – 39.66
	AUC_{0-24} (ng*hr/mL)	27	520.980	773.864	67.32	63.42 – 71.46

Nal SR/Bup SR q12h: Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets q12h (Predicted Test, Treatment D)
Nal IR q24h: One Naltrexone IR 50 mg Tablet q24h (Predicted Reference, Treatment E)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

Analyte	Pharmacokinetic Parameter	N	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Interval
			Nal SR/Bup SR q12h	Bup SR q12h		
Bupropion	$C_{max,ss}$ (ng/mL)	27	218.699	285.148	76.70	70.41 – 83.55
	AUC_{0-12} (ng*hr/mL)	27	1595.898	1976.153	80.76	74.96 – 87.00
Hydroxybupropion	$C_{max,ss}$ (ng/mL)	27	1696.365	2004.985	84.61	78.94 – 90.68
	AUC_{0-12} (ng*hr/mL)	27	19111.762	22402.787	85.31	79.66 – 91.36
Threohydrobupropion	$C_{max,ss}$ (ng/mL)	27	541.963	617.763	87.73	83.10 – 92.62
	AUC_{0-12} (ng*hr/mL)	27	6033.901	6818.317	88.50	83.79 – 93.46
Erythrohydrobupropion	$C_{max,ss}$ (ng/mL)	27	95.805	110.541	86.67	81.40 – 92.28
	AUC_{0-12} (ng*hr/mL)	27	1070.838	1215.827	88.07	82.70 – 93.79
PAWC	$C_{max,ss}$ (µM/mg)	27	5.593	6.695	83.54	78.40 – 89.02
	AUC_{0-12} (µM*hr/mg)	27	58.917	69.441	84.84	79.79 – 90.22

Nal SR/Bup SR 12qh: Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets Q12H (Treatment D, Predicted Test)
Bup SR q12h: One Bupropion SR 200 mg Tablet Q12H (Treatment F, Predicted Reference)
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

Conclusions:

The 2 x NB 8/90 mg was bioequivalent to bupropion SR 150 mg for bupropion total and peak exposures. The naltrexone total and peak exposures were significantly lower than the 50 mg naltrexone IR formulation. The steady-state bupropion exposure was predicted to be ~ 20% lower for 2 x NB 8/90 mg than that from 200 mg bupropion SR after BID administration. The steady-state naltrexone total exposure was predicted to be 40% lower than naltrexone IR 50 mg daily dose.

1.1.2 PKPD (IR-PET)

Administration of a single oral dose of 50 mg naltrexone has been reported in literature to result in > 80% receptor blockade for up to 72 hours. Therefore, to understand the PKPD relationship and to optimize the naltrexone doses for the Contrave program, this study was conducted to answer the question: "What is the relationship between % CNS opioid receptor occupancy and naltrexone dose/concentration?".

The study design is as follows:

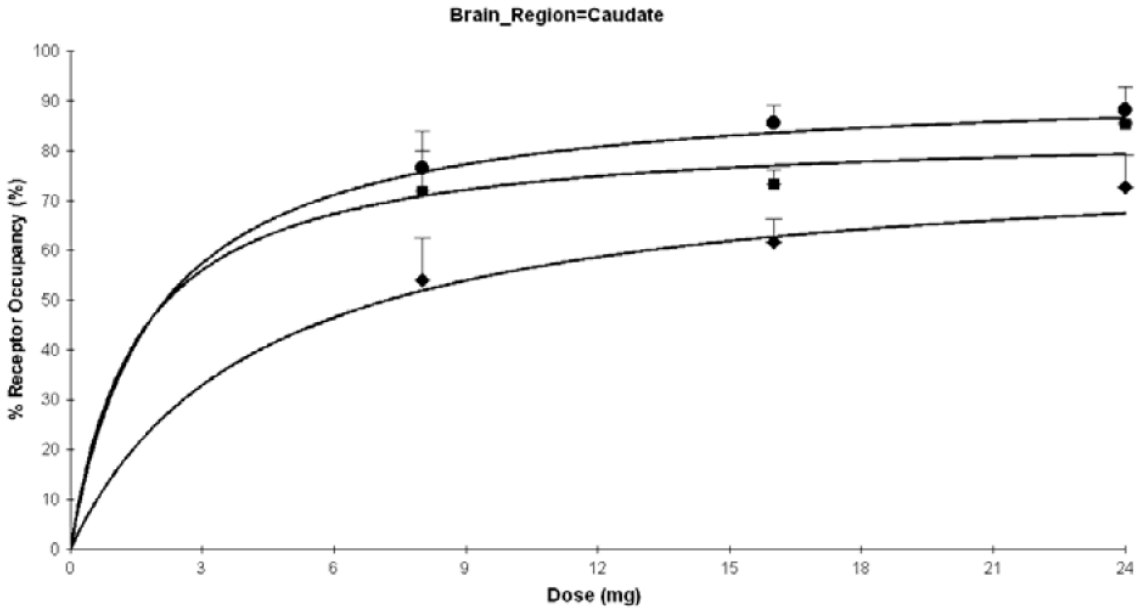
Title	Single Center, Open Label, Clinical Pharmacology Study to Determine the Dose/Response of CNS Receptor Occupancy by Naltrexone
Objectives	• To characterize the dose response curve of naltrexone on receptor occupancy. • To define the dose response of naltrexone on the occupancy of CNS receptors and identify doses which result in > 80% occupancy. • To correlate the dose response of CNS receptors by naltrexone with plasma levels of naltrexone and 6-beta naltrexol
Study Design	This clinical study was conducted as an open label, 7-day dosing PET study in healthy but overweight or obese subjects. Nine (9) healthy but overweight or obese subjects (BMI >25, kg/m^2) were enrolled. After obtaining informed consent, a thorough screening evaluation was performed, including medical history, physical examination including vital signs, an electrocardiogram (ECG), clinical laboratory tests, and a magnetic resonance imaging (MRI) scan. For female subjects, a blood sample was drawn for serum β-hCG assay (pregnancy test) at screening. Once all screening procedures were performed, and if the subject met all inclusion and exclusion criteria, they were enrolled into the study. Subjects then had a baseline PET scan. After completion of the baseline PET scan, each subject was assigned to one of three dosing cohorts. Drug was taken orally, twice a day with a meal, beginning the day after baseline PET scan on Day 1. Dosing continued until Day 7. On the afternoon of Day 6, each subject was asked to check into a hotel near PET center. The Day 7 morning dose was administered at the PET center. Afterwards, the 1-hour, 6-hour, and 24-hour post-dose PET scans were performed on Days 7 and 8.
Study Population	N= 9 Healthy obese subjects, Gender: 7 M and 2 F, Age: 19-54 yr BMI: >25, kg/m^2
Test Product	Naltrexone was administered as powder-filled gelatin capsules for 7 days
Radiotracer for PET Imaging	[^{11}C]DIPRENORPHINE (DPN): Diprenorphine (DPN) is an opioids antagonist that was originally developed for use in veterinary medicine to reverse the effects of narcotic sedatives in large animals. DPN is selective for the opioid system, showing negligible affinity for other classes of cellular receptors. [^{11}C]Carfentanil (CFN) had been previously used to image mu opiate receptors. DPN differs from CFN in that DPN is an antagonist and labels delta and kappa opiate receptors in addition to mu opiate receptors; specifically, DPN will label all three opiate receptors, while, CFN is specific for the mu opiate receptor. Advantages of DPN over CFN are the absence of pharmacologic effects at the dose administered to human subjects and the possibility of imaging delta and kappa opiate receptors.

Dosing Groups	Three subjects participated in each of the following dosing cohorts: Group A: 8 mg b.i.d. (total daily dose - 16 mg) Group B: 16 mg b.i.d. (total daily dose - 32 mg) Group C: 24 mg b.i.d. (total daily dose - 48 mg)
Sampling: Blood	Blood samples for determination of naltrexone and 6-beta-naltrexol, were collected at the following times for each treatment: 1, 6, and 24 hours post-dose.
Urine	none
Feces	none
PK Assessments	Naltrexone concentrations
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	% Receptor occupancy Emax, ED50, EC50

Protocol Deviations:
There were no notable protocol deviations. There were deviations related to laboratory chemistry values, which are not expected to affect the PKPD results in any way.

Pharmacodynamic Results:
A representative dose-response plot for the Caudate region in brain is presented below:

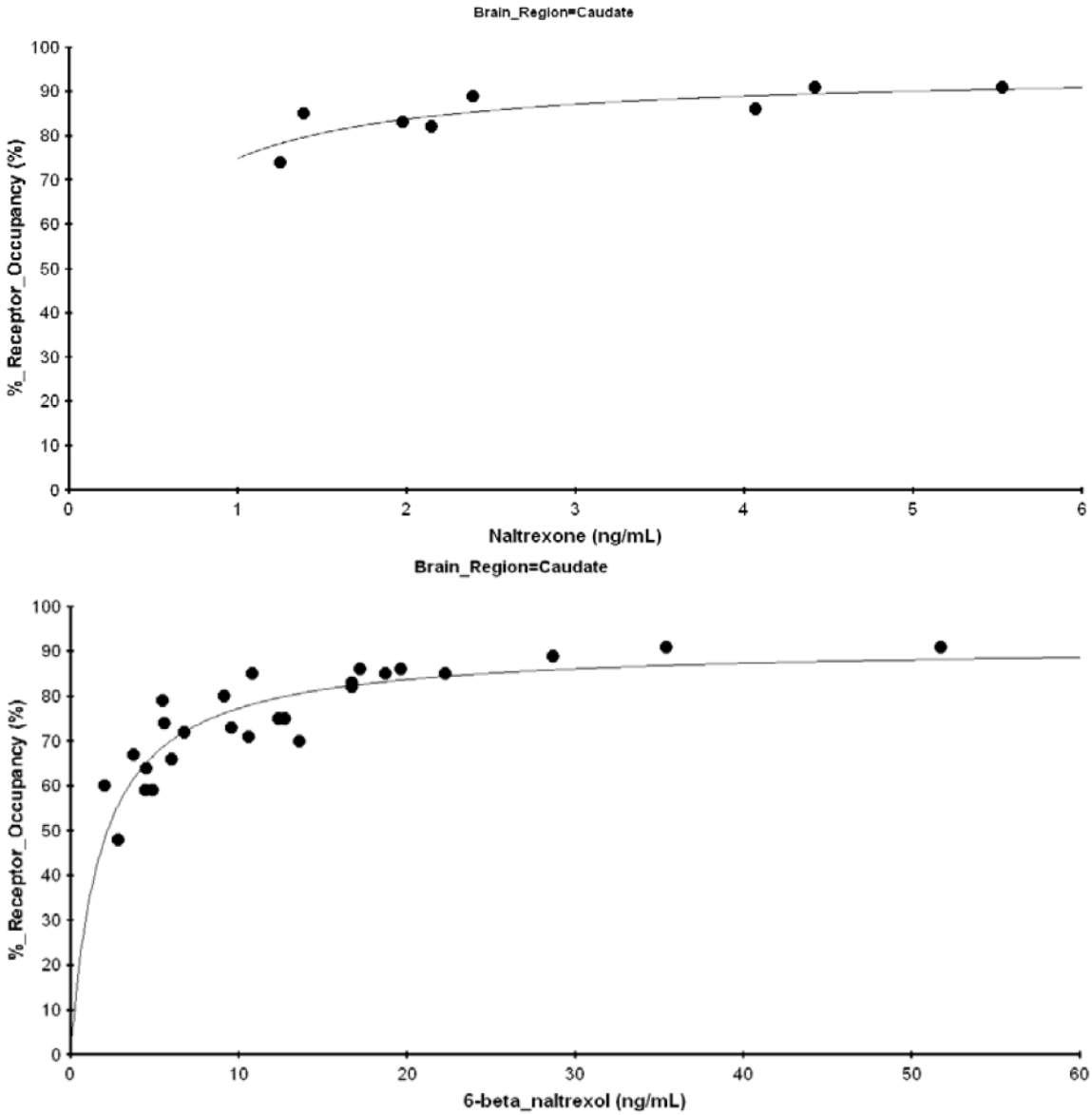
Figure 1 Percent Opioid Receptor Occupancy (%RO) in Caudate Versus Naltrexone Dose



The following relationship was used to explore dose/concentration response for receptor occupancy:

$$\%\mathrm{Re}\,ceptorOccupancy = \frac{100 \times AnalyteConcentration}{EC_{50} + AnalyteConcentration}$$

Figure 1 Percent Opioid Receptor Occupancy (%RO) in Caudate Versus Naltrexone and 6beta-naltrexol



These Emax models assume oral administration of naltrexone, and do not imply causality, as the relative contribution of naltrexone and 6-beta naltrexol to receptor occupancy cannot be ascertained. Based on these Emax models, an average naltrexone concentration of 2 ng/mL over 24 hours would be correlated with an average 85% receptor occupancy. This correlation is less reliable than the 6-beta naltrexol correlation due to the number of samples that were below the limit of quantitation for this analyte. Based on these Emax models, an average 6-beta naltrexol concentration of 15 ng/mL over 24 hours would be correlated with an average 85% receptor occupancy. In addition, a 12-hr 6-beta naltrexol concentration of 20 ng/mL would be correlated with an average 85% receptor occupancy. Estimates/predictions were necessary to understand receptor occupancy at 12 hours, since no direct measurements were made at this time point.

The summary of receptor occupancy by dose and time is presented in the Table below:

Table 1 Average Receptor Occupancy in the entire brain as a function of BID dose (mg) and time, including upper and lower 90% Confidence Intervals

Dose (mg)	Time (hr)	Mean	SD	90% CI Lower	90% CI Upper
8	1	74.63	4.03	72.13	77.13
	6	70.70	4.34	68.01	73.39
	24	53.50	5.74	49.94	57.06
16	1	88.37	4.30	85.71	91.03
	6	76.70	4.11	74.16	79.25
	24	64.37	4.88	61.34	67.40
24	1	87.59	3.68	85.31	89.88
	6	84.96	4.34	82.27	87.65
	24	74.19	5.43	70.82	77.55

Conclusions:

Doses significantly lower than the current clinical dose of naltrexone 50 mg QD can achieve receptor occupancy of greater than 70%. Naltrexone twice daily dosing for 7 days resulted in average receptor occupancy in excess of 80% with 24 mg and for between 1 to 6 hours with 16 mg. Average receptor occupancy with 8 mg naltrexone twice daily was greater than 70% for at least 6 hours. At 16 and 24 mg twice daily, the receptor occupancy remains above 60% up to 24 hours. The dose-occupancy curve indicates that a saturating occupancy can be achieved. Naltrexone shows uniform occupancy across brain regions, no meaningful differences in receptor occupancy between regions were observed. The sponsor's assessments and conclusions are acceptable.

1.1.3 PKPD (NB-222)

Based on the results from study IR-PET, which provided insight into the PKPD relationship for naltrexone IR, this study further evaluated the same relationship for a controlled release form of naltrexone. Therefore, this study was conducted to answer similar question: "What is the relationship between % CNS opioid receptor occupancy and dose/concentration of naltrexone given as a controlled release formulation?".

The study design is as follows:

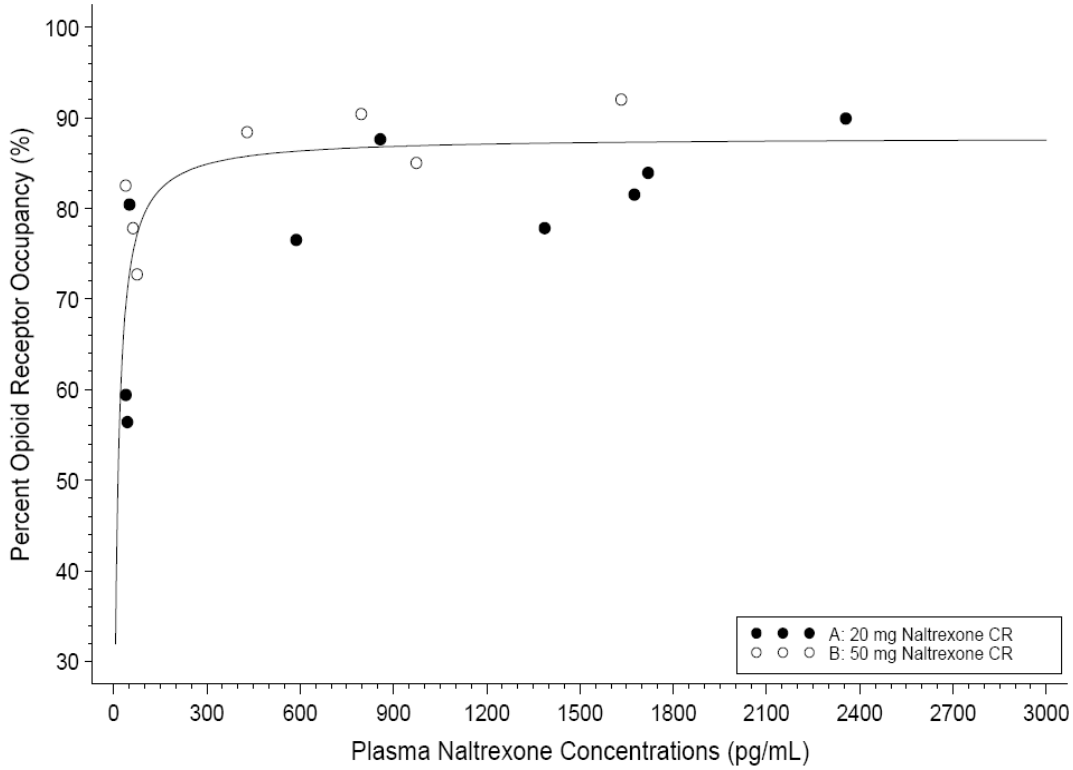
Title	Single-Center, Phase 1, Open-Label, Clinical Pharmacology Study to Determine the CNS Receptor Occupancy by Controlled-Release Naltrexone
Objectives	The primary objectives of this study were to characterize the influence of 2 doses of a controlled release (CR) naltrexone formulation on opioid receptor occupancy and to correlate the response of central nervous system (CNS) receptors by naltrexone/6-beta naltrexol with plasma levels of naltrexone and 6-beta naltrexol.
Study Design	This clinical study was conducted as an open-label, Positron Emission Tomography (PET) study in healthy, obese subjects. Eligible subjects were sequentially assigned to 1 of 2 dosing groups in which naltrexone CR was taken orally twice daily (BID) with food from Days 1 to 6. The final dose of study medication was administered the morning of Day 7. PET scans were performed and blood samples for pharmacokinetic (PK) analysis were collected at Days 0 (baseline), 7, and 8.
Study Population	N= 7 Healthy obese subjects, Gender: 3 M and 4 F, Age: 29 (20-50 yr) BMI: 33 (29 – 42) kg/m^2
Test Product	The test product was naltrexone CR administered orally
Radiotracer for PET Imaging	Approximately 20 mCi of [11C] diprenorphine (DPN) was administered to each subject through intravenous (IV) injection prior to the beginning of each PET scan.
Dosing Groups	Three subjects participated in each of the following dosing cohorts: • Dose Group A: 2 × 5 mg minitabs BID for a 20 mg total daily dose • Dose Group B: 5 × 5 mg minitabs BID for a 50 mg total daily dose (Subject 15 in Dose Group B received 5 × 6 mg minitabs QD in the morning and 4 × 5 mg minitabs QD in the evening) for a 50 mg total daily dose.
Sampling: Blood	Pharmacokinetics: Plasma concentrations of naltrexone and 6-beta naltrexol were measured prior to each PET scan on Day 0 (baseline), and on Day 7 at approximately 1, 5.5, and 25 hours (Day 8) post-dose.
Urine	none
Feces	none
PK Assessments	Naltrexone concentrations
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	PET scans were performed immediately following IV administration of approximately 20 mCi of [11C]DPN on Day 0 (baseline) and on Day 7 at 1, 5.5, and 25 hours (Day 8) after administration of the last naltrexone dose on the morning of Day 7. The percent opioid receptor occupancy (%RO) was calculated from the binding potential (BP) data ([pre-treatment BP – post-treatment BP]/pre-treatment BP) in each of the following brain regions: caudate, cingulate cortex, orbital frontal cortex, parietal cortex, prefrontal cortex, putamen, superior frontal cortex, temporal cortex, and thalamus.

Protocol Deviations:
Drug was dispensed to 2 subjects who were not able to complete the study, which depleted drug supply at the site for the doses needed for Subject 15. A protocol deviation was granted by the Sponsor to allow for an alternate dosing schedule for this subject. Subject 15 received 5 × 6 mg minitabs QD in the morning and 4 × 5 mg minitabs QD in the evening for Days 1 through 6. Subject 15 also received 5 × 6 mg minitabs the morning of Day 7. The subject received a total daily dose of 50 mg on Days 1 through 6 as was specified by the protocol.

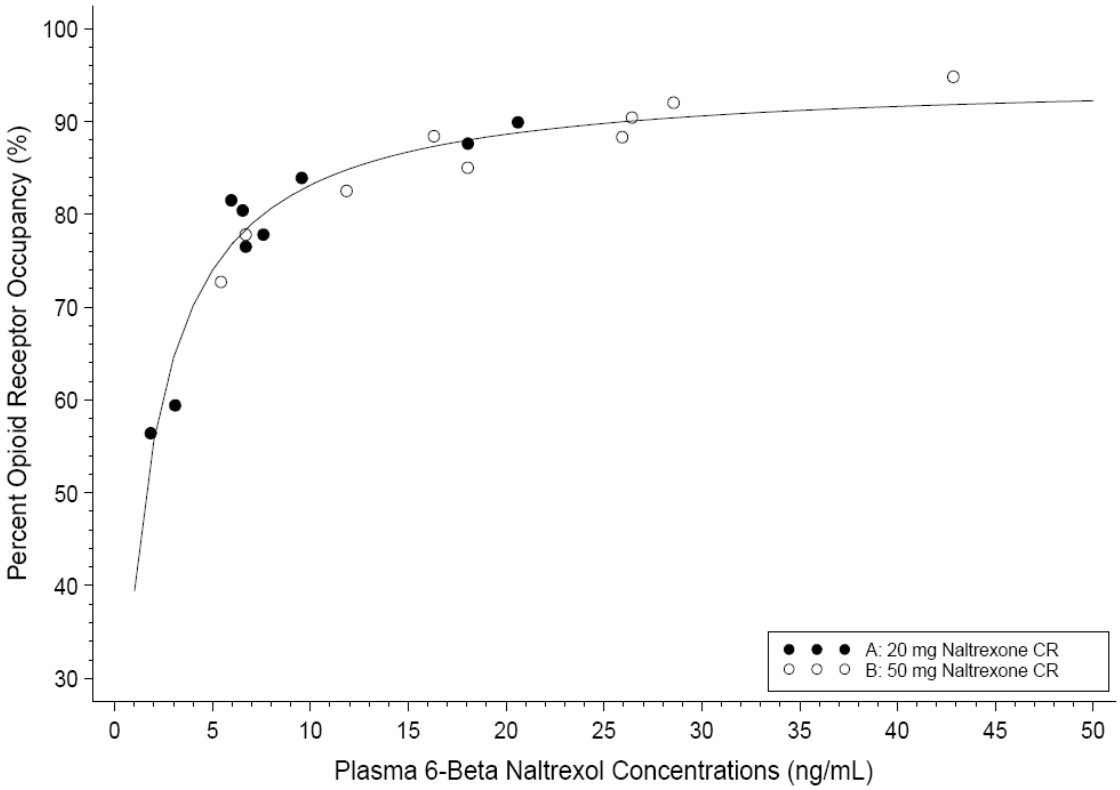
Pharmacodynamic Results:

A representative PKPD plot for the Frontal Cortex region in brain is presented below:

Figure 1 Percent Opioid Receptor Occupancy (%RO) in Superior Frontal Cortex Versus Plasma Naltrexone and 6-Beta Naltrexol



Solid line represents model-predicted concentration-response relationship:
E = (Emax*C)/(EC50+C)



Solid line represents model-predicted concentration-response relationship:
E = (Emax*C)/(EC50+C)

The summary of receptor occupancy by region, treatment and time is presented in the Tables below:

Table 1 Percent Opioid Receptor Occupancy (%RO) by Region of Interest and Time for Dose Groups A and B and final PD parameters

Percent Opioid Receptor Occupancy (%RO) by Region of Interest and Time for Dose Groups A and B

	% Opioid Receptor Occupancy					
	Nal CR 20 mg (N = 3)			Nal 50 mg (N = 3)		
Region Of Interest	**1 hr**	**5.5 hr**	**25 hr**	**1 hr**	**5.5 hr**	**25 hr**
Caudate	81.7 ± 4.8	77.3 ± 7.6	55.4 ± 20.0	87.0 ± 2.5	85.8 ± 4.3	74.3 ± 2.3
	(79.1)	(73.4)	(52.6)	(87.4)	(83.6)	(75.3)
Cingulate Cortex	79.7 ± 6.1	76.0 ± 7.4	64.3 ± 12.1	84.2 ± 2.7	80.7 ± 4.8	72.5 ± 2.9
	(78.7)	(72.2)	(62.4)	(82.6)	(81.7)	(73.1)
Orbital Frontal Cortex	82.8 ± 4.7	78.3 ± 6.5	68.5 ± 10.4	86.7 ± 0.9	84.5 ± 5.4	75.5 ± 5.7
	(80.5)	(76.5)	(67.8)	(86.9)	(82.2)	(73.4)
Parietal Cortex	83.1 ± 5.5	79.1 ± 8.0	66.5 ± 14.0	90.0 ± 4.8	86.2 ± 5.5	76.8 ± 3.9
	(81.4)	(75.6)	(59.2)	(87.8)	(83.4)	(77.5)
Prefrontal Cortex	84.8 ± 4.1	80.1 ± 6.3	65.0 ± 14.2	92.4 ± 5.1	88.6 ± 5.4	80.6 ± 5.6
	(83.0)	(77.5)	(57.2)	(89.7)	(90.9)	(83.5)
Putamen	75.6 ± 6.0	71.3 ± 8.2	53.7 ± 15.1	78.6 ± 1.6	76.5 ± 6.5	63.1 ± 4.9
	(73.3)	(68.1)	(46.9)	(78.3)	(74.5)	(62.0)
Superior Frontal Cortex	85.1 ± 4.3	80.6 ± 6.1	65.4 ± 13.1	90.5 ± 3.7	89.1 ± 3.7	77.7 ± 4.9
	(83.9)	(77.8)	(59.4)	(88.4)	(90.4)	(77.8)
Temporal Cortex	82.0 ± 3.4	77.6 ± 5.9	65.5 ± 9.7	86.1 ± 2.5	84.1 ± 4.4	76.5 ± 4.4
	(80.3)	(74.7)	(61.5)	(84.6)	(83.3)	(77.4)
Thalamus	89.2 ± 5.4	86.2 ± 4.9	72.3 ± 11.5	91.6 ± 1.3	89.1 ± 4.7	80.7 ± 3.8
	(92.0)	(87.7)	(78.2)	(92.2)	(88.0)	(80.6)

Values are presented as Mean ± SD (Median).
Note: Time points are in relation to the last dose of naltrexone administered on Day 7.
Nal CR 20 mg = 20 mg naltrexone CR minitabs (2 × 5 mg BID), Dose Group A
Nal CR 50 mg = 50 mg naltrexone CR minitabs (5 × 5 mg BID or 5 × 6 mg QD am and 4 × 5 mg QD pm for Subject 15 only), Dose Group B

Table 2 Final PD parameters

Parameters for the Final Simple E_{max} Model for Each Brain Region by Analyte

	Naltrexone			6-Beta Naltrexol		
Region Of Interest	E_{max} ± SD (%)	EC_{50} ± SD (pg/mL)	EC_{90} (pg/mL)	E_{max} ± SD (%)	EC_{50} ± SD (ng/mL)	EC_{90} (ng/mL)
Caudate	86.24 ± 3.81	15.8 ± 4.90	143.03	92.26 ± 4.04	1.71 ± 0.38	15.41
Cingulate Cortex	81.34 ± 2.22	8.82 ± 2.68	79.34	86.96 ± 1.35	1.18 ± 0.12	10.62
Orbital Frontal Cortex	84.31 ± 1.98	8.37 ± 2.28	75.37	87.61 ± 2.29	0.82 ± 0.19	7.37
Parietal Cortex	86.15 ± 2.63	9.51 ± 3.04	85.58	92.19 ± 2.01	1.24 ± 0.17	11.19
Prefrontal Cortex	88.36 ± 3.02	9.99 ± 3.43	89.95	95.74 ± 2.11	1.43 ± 0.18	12.85
Putamen	77.75 ± 2.78	15.93 ± 3.97	143.37	84.52 ± 3.01	1.78 ± 0.31	16.01
Superior Frontal Cortex	87.84 ± 2.65	10.50 ± 3.06	94.52	94.82 ± 1.42	1.41 ± 0.12	12.65
Temporal Cortex	83.63 ± 2.07	8.49 ± 2.42	76.41	88.62 ± 1.38	1.06 ± 0.12	9.50
Thalamus	89.89 ± 2.04	7.95 ± 2.19	71.59	94.64 ± 1.84	0.94 ± 0.14	8.46

Conclusions:

- Using [11C]DPN PET to quantify %RO showed that the opioid receptor occupancy by naltrexone was rapid, with the highest %RO at 1 hour post-dose and values generally above 80% in most brain regions for both the 20 and 50 mg daily naltroxone CR doses.

- Overall, %RO values were slightly higher in all brain regions at all 3 imaging time points following the 50 mg daily doses than with 20 mg daily doses.

- By 25 hours post-dose, there was still substantial naltrexone receptor occupancy in most brain regions, with 70% to 80% occupancy following the 50 mg daily dose and 53% to 72% occupancy following the 20 mg daily dose.

- The relationship between %RO in each brain region and 6-beta naltrexol concentrations was best described by a simple Emax model, with predicted Emax values in the 85% to 96% range. The relationship between %RO in each brain region and naltrexone concentrations was also best described by a simple Emax model; however, the predicted Emax values tended to be underestimated relative to the highest mean %RO values observed at 1 hour following 50 mg daily doses. Predicted Emax values were in the 78% to 90% range with EC90 values ranging from 0.07 to 0.14 ng/mL.

Reviewer's Comments: The sponsor's assessments and conclusions from this study are acceptable. Though, the two studies (NB-222 and IR-PET) were conducted in a small number of subjects, the results from these studies appear to be supportive of sponsor's decision to select 16 mg and 32 mg total naltrexone daily dose for clinical evaluation.

1.1.4 BE-Evaluations (NB-228, 229)

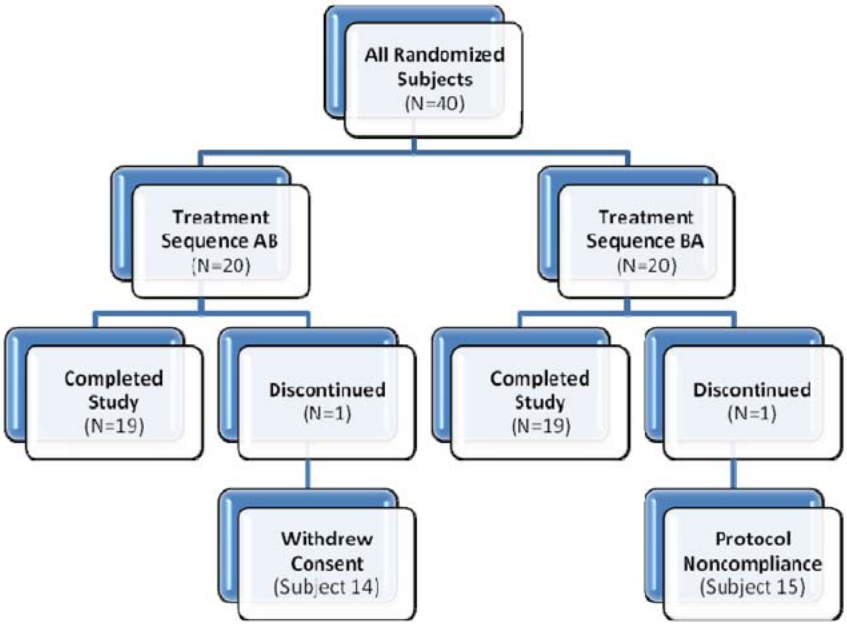
NB-228:
The study details are as follows:

Title:	A Phase 1, Bioequivalence Study of Two Different Formulations of Naltrexone SR/Bupropion SR Combination Trilayer Tablets Under Fasting Conditions
Objectives:	**Primary:** To establish the bioequivalence of a single dose trilayer tablet containing sustained release naltrexone (naltrexone SR) and sustained release bupropion (bupropion SR) produced by the (b) (4) at (b) (4) and the (b) (4) relative to a single dose trilayer tablet containing sustained release naltrexone (naltrexone SR) and sustained release bupropion (bupropion SR) manufactured at (b) (4) **Secondary:** To evaluate the safety and tolerability of the trilayer (naltrexone SR + bupropion SR) formulation based on spontaneously reported adverse events (AEs).
Study Design	This was a Phase 1, single-center, open, randomized, single oral dose, 2-way crossover study to assess the bioequivalence of 2 different formulations of naltrexone SR/bupropion SR combination trilayer tablets under fasting conditions in healthy adult subjects. The 2 study treatments (A and B) were as follows: A = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets manufactured by (b) (4) s (Reference) B = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets manufactured by (b) (4) (Test) Prior to administration of study medication, each subject was randomly assigned to 1 of 2 treatment sequences. The treatment sequence for each subject included both treatments (A and B). Subjects checked into the study center the day prior to dosing. Following an overnight fast of at least 10 hours, subjects were given 2 tablets of Treatment A or Treatment B with 240 mL (8 fluid ounces) of water (total daily dose of 16 mg naltrexone SR/180 mg bupropion SR). No food was allowed for at least 4 hours postdose.
Study Population	N= 40 Healthy subjects, Gender: 20 M and 20F, Age: 33 (19-58) yr Weight: 154 (107-200) lb, BMI: 24 (19-27)
Test Product	The test product was naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets (Treatment B, Test), Lot number C7F0087, manufactured by (b) (4) given as a single oral dose with 240 mL of water.
Reference Products	The reference product was naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets (Treatment A, Reference), Lot number B07084, manufactured by (b) (4), given as a single oral dose with 240 mL of water.
Sampling: Blood	The administration of study drug in each period was separated by a 9-day washout period between dosing days. In each period, a total of 18 blood samples were drawn from each subject. Serial blood samples were

	collected at 0 hr (predose) and at 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours postdose. On each test day, subjects had blood samples taken for quantitation of naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞,Cmax, Tmax, Kel, t1/2
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Protocol Deviations: There were no protocol deviations with respect to study entry criteria, no subjects who developed withdrawal criteria and were not withdrawn, and no subjects who received the wrong treatment or incorrect dose.

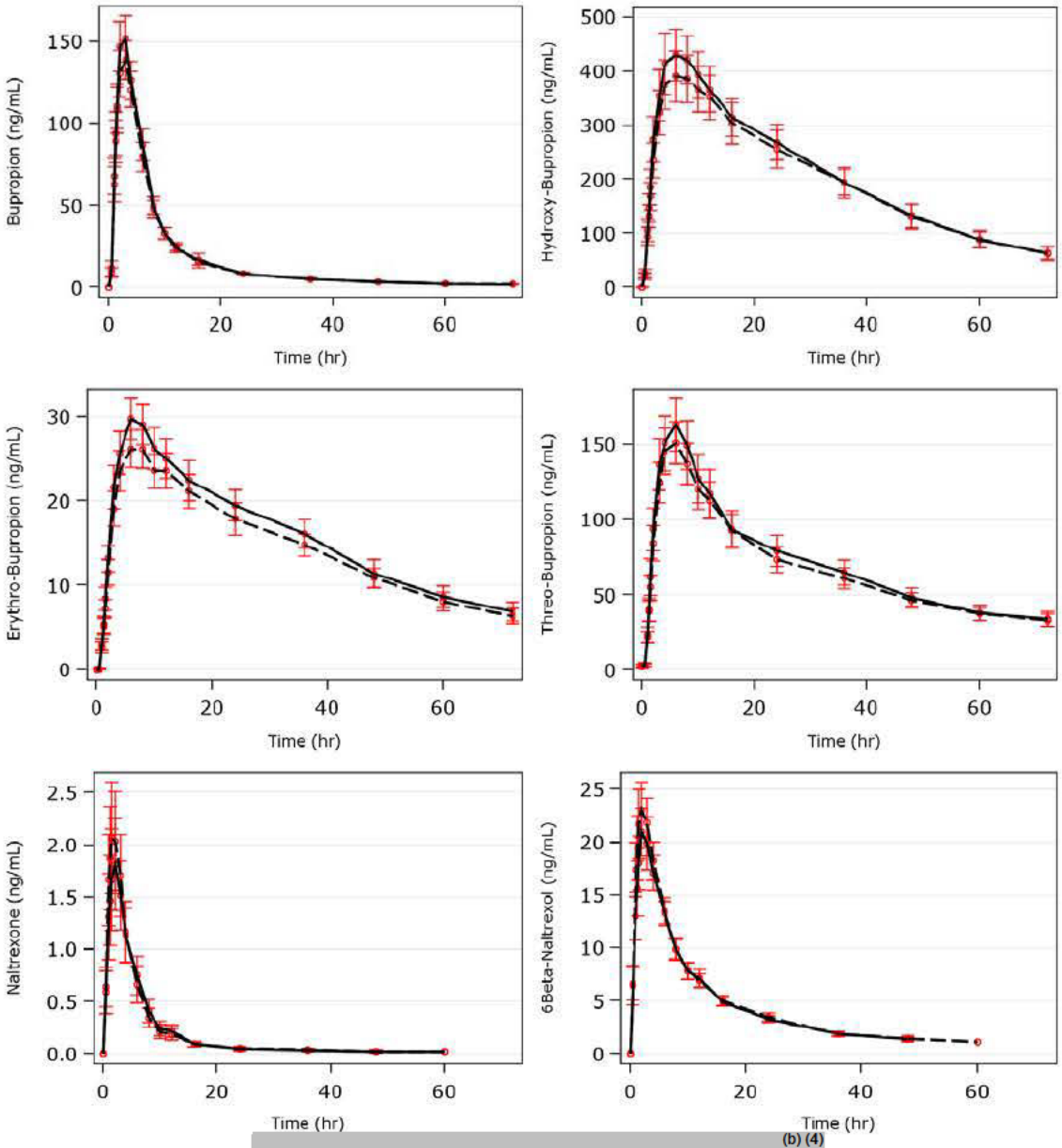
Subject Disposition and Data Sets Analyzed:
A total of 40 healthy male and female subjects were planned and enrolled in the study; 38 subjects completed the study. All 40 subjects were included in the safety analysis, and 39 subjects were included in the PK analysis. Three subjects were excluded from individual treatment summary statistics and statistical analysis.



Subject 25 was excluded from the PK summary statistics and statistical analysis for both treatments due to vomiting after treatment with both formulations ((b) (4) and therefore did not have evaluable PK parameters. Two subjects were excluded from PK summary statistics and statistical analysis for one treatment, but still provided data for the other treatment. Subject 14 discontinued prior to receiving the second formulation (b) (4) Subject 15 was discontinued from the study prior to receiving the second formulation (b) (4). Subject 15 also vomited 24 hours and 43 minutes after receiving the first formulation (b) (4); however, since the emesis

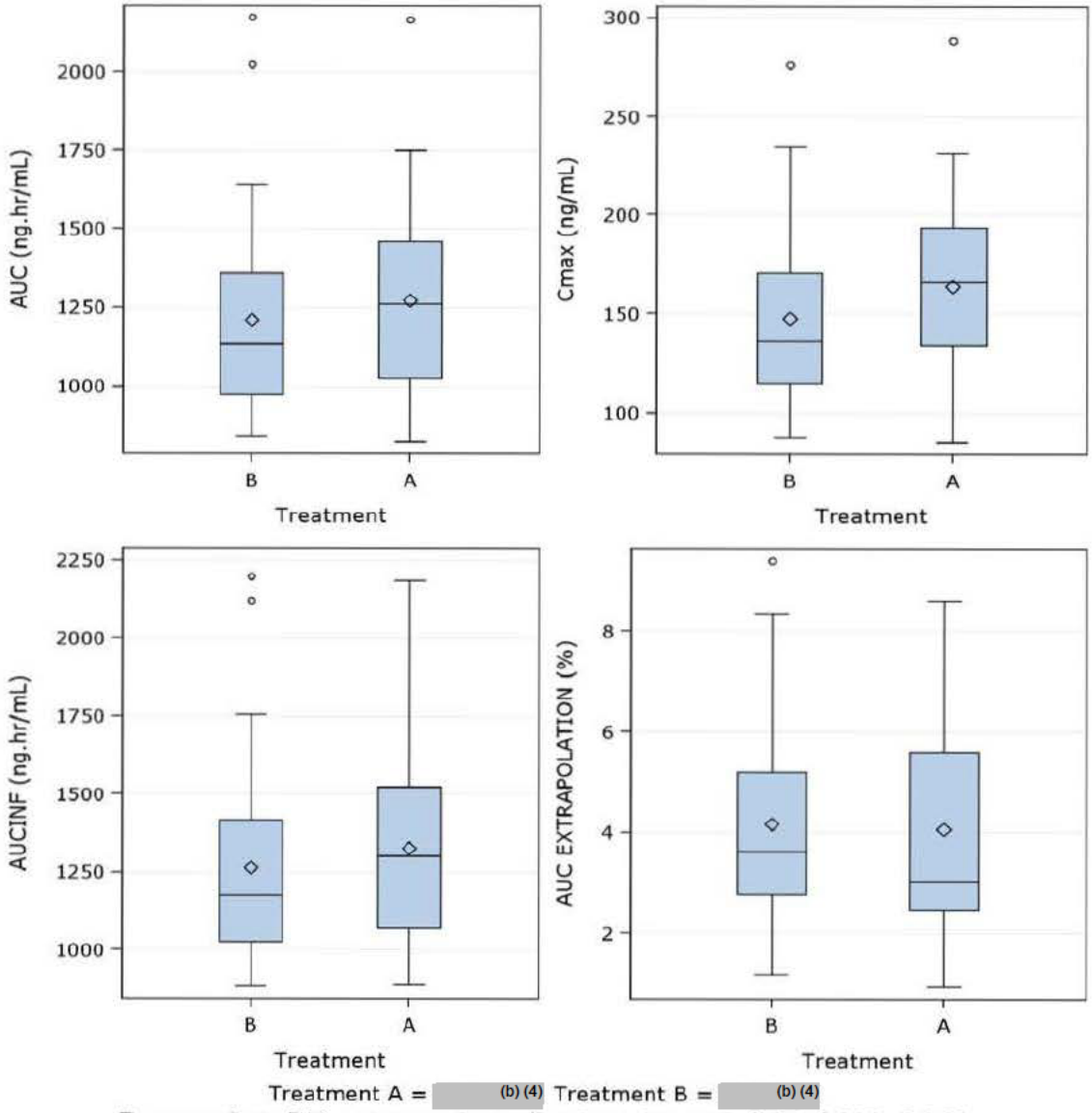
occurred after the 24-hour dosing interval, this subject was included in the statistics and statistical analysis of PK for this treatment.

Pharmacokinetic Results:
The concentration-time profiles of all analytes by treatment are shown in Figure below:



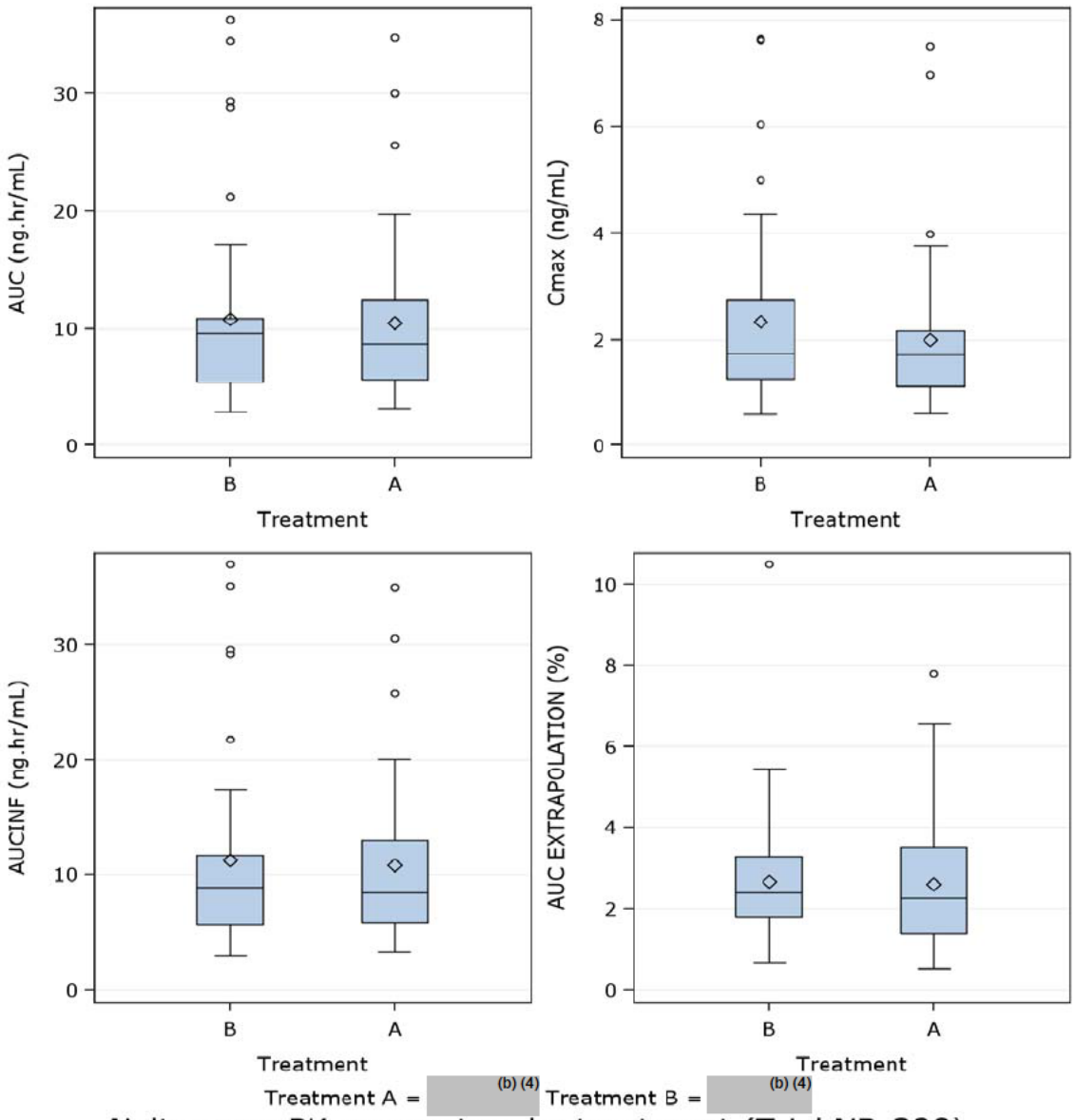
Mean(±)SE Concentration-time plots by treatment (Trial NB-228)

The distribution of PK parameters by treatment [redacted] (b) (4) for naltrexone and bupropion is summarized in the figures below:



Treatment A = [redacted] (b) (4) Treatment B = [redacted] (b) (4)

Bupropion PK parameters by treatment (Trial NB-228)



Naltrexone PK parameters by treatment (Trial NB-228)

The AUC % extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both naltrexone and bupropion.

The statistical comparison of PK parameters of naltrexone and bupropion are given in the following tables:

Table 1 Statistical comparison for naltrexone PK parameter [redacted]

Statistical Comparison of Naltrexone PK Parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A- [redacted]	B- [redacted]	AUC(0-inf)	ng.hr/mL	96.45	90.47 - 102.83
		AUC(0-t)	ng.hr/mL	95.78	90 - 101.92
		Cmax	ng/mL	84.46	77.17 - 92.44

Table 2 Statistical comparison for bupropion PK parameter, [redacted]

Statistical Comparison of Bupropion PK Parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
A- [redacted]	B- [redacted]	AUC(0-inf)	ng.hr/mL	105.49	101.05 - 110.12
		AUC(0-t)	ng.hr/mL	105.47	101.05 - 110.08
		Cmax	ng/mL	111.59	105.57 - 117.95

Reviewer's Conclusions/Comments:

The study results show that:

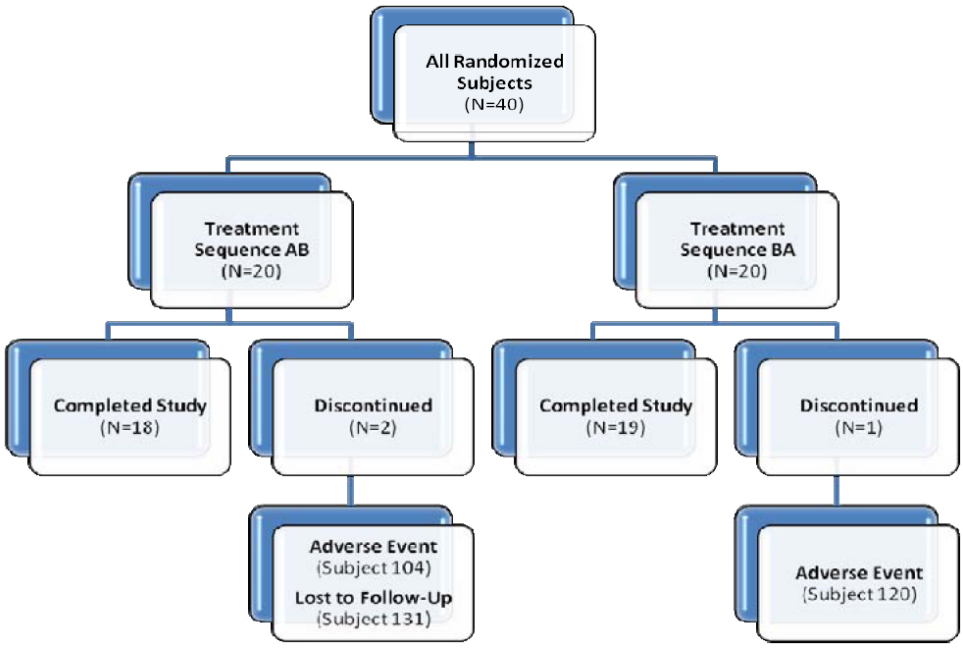
- 90% CI for plasma naltrexone AUC0-t and AUC0-inf were within the 80 - 125% range. This indicates the extent of naltrexone exposure from the [redacted] test trilayer tablets was bioequivalent to the [redacted] reference trilayer tablets.
- Geometric LS means plasma naltrexone Cmax for the [redacted] test trilayer tablets was slightly lower (by approximately 15%) than the [redacted] reference trilayer tablets, with the lower bound of the 90% CI (77%) just below the 80% required for bioequivalence. The sponsor's conclusion of the lower naltrexone Cmax being [redacted] does not go well with their rationale that [redacted]
- The 90% CIs for plasma bupropion Cmax, AUC0-t, and AUC0-inf were within the 80 - 125% range, indicating the peak and overall bupropion exposures from the [redacted] test trilayer tablets were bioequivalent to the [redacted] reference trilayer tablets.
- These results are acceptable.

NB-229:
The study details are as follows:

Title:	A Phase 1, Open-Label, Randomized, Single-Dose, Two-Way Crossover Study to Assess the Bioequivalence of 2 Different Naltrexone SR 8 mg/Bupropion SR 90 mg Combination Trilayer Tablets in Healthy Adult Subjects
Objectives:	To assess the bioequivalence of 2 different naltrexone sustained release (SR)/bupropion SR combination trilayer tablets.
Study Design	The 2 study treatments (A and B) were as follows: A = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets Manufactured by (b) (4) (Reference treatment) B = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets Manufactured by the (b) (4) (Test treatment) Prior to the start of the study, each subject was randomly assigned to 1 of 2 treatment sequences (i.e., AB or BA). The treatment sequence for each subject included both treatments: Treatment A (Reference) and Treatment B (Test). Following an approximately 10-hour fast, subjects received a single oral dose of study drug on Day 1 of each period, with a minimum 14-day washout period between dosing days.
Study Population	N= 40 Healthy subjects, Gender: 23 M and 17F, Age: 33 (19-60) yr Weight: 172 (126-249) lb, BMI: 26 (19-34)
Test Product	The test treatment in this study was 2 naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets manufactured by the (b) (4) given as a single oral dose with 240 mL of water. (b) (4) and (b) (4) were also involved in the manufacturing of the tablets. The test treatment is referred to as (b) (4) to differentiate it from clinical trial material manufactured (b) (4) used in other studies. Lot number B07018 was used.
Reference Products	The reference treatment in this study was 2 naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets manufactured by (b) (4) given as a single oral dose with 240 mL of water. Lot number C8A0139 was used.
Sampling: Blood	The administration of study drug in each period was separated by a 14 - day washout period between dosing days. In each period, a total of 18 blood samples were drawn from each subject. Serial blood samples were collected at 0 hr (predose) and at 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours postdose. On each test day, subjects had blood samples taken for quantitation of naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞,Cmax, Tmax, Kel, t1/2
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Protocol Deviations: There were no protocol deviations with respect to study entry criteria, no subjects who developed withdrawal criteria and were not withdrawn, and no subjects who received the wrong treatment or incorrect dose.

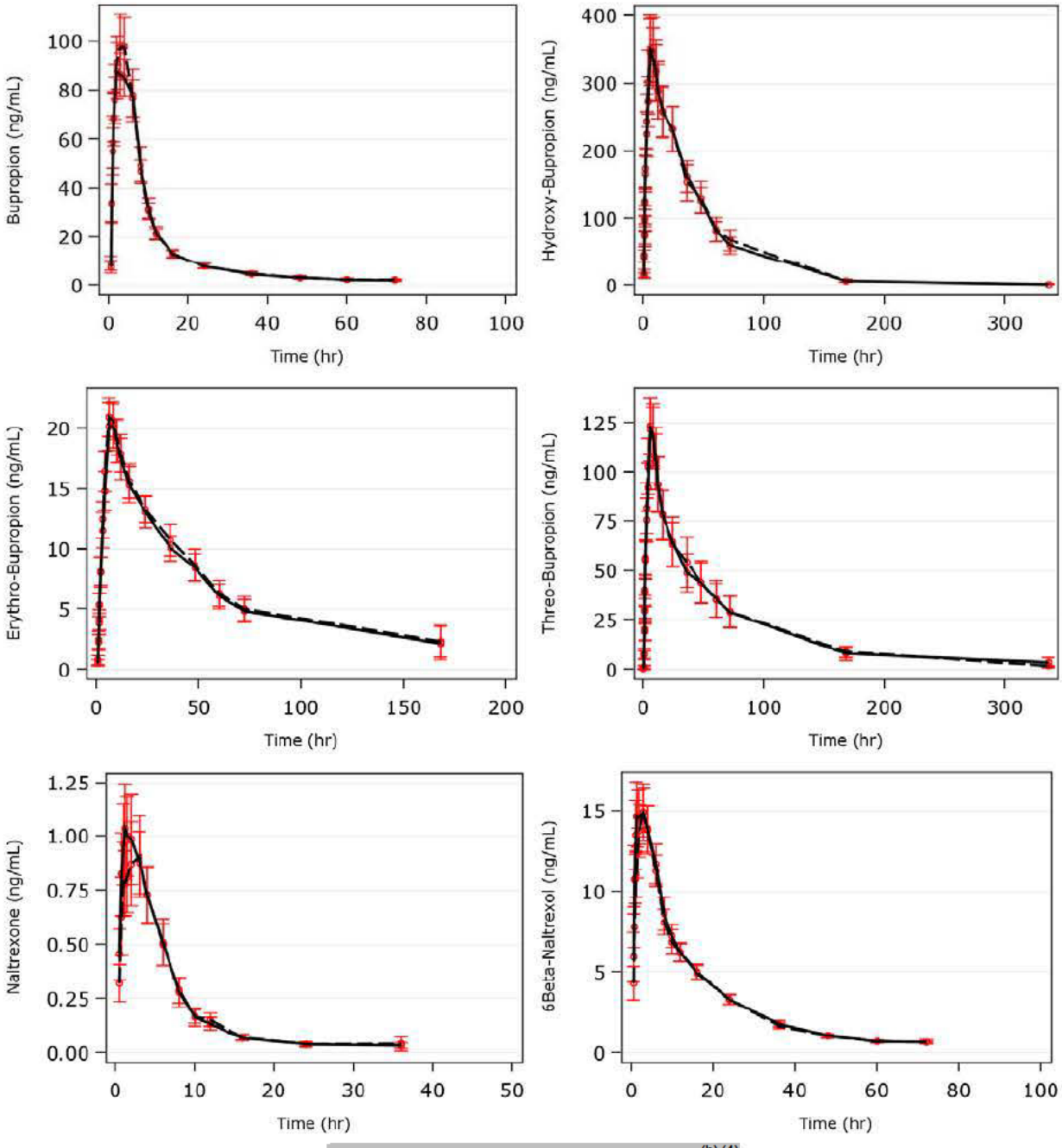
Subject Disposition and Data Sets Analyzed:
A total of 40 healthy male and female subjects were planned and enrolled in the study; 38 subjects completed the study. All 40 subjects were included in the safety analysis, and 39 subjects were included in the PK analysis. A total of 40 subjects entered the study and were randomized to 1 of 2 treatment sequences. A total of 37 subjects completed the study (Table 14.1.1.1). Two subjects were discontinued due to AEs. Subject 104 was discontinued due to the AE of moderate nausea on Day 1 of Period 1 following administration of one of the treatments (b) (4) reference trilayer tablets). Subject 120 was discontinued at check-in for Period 2 due to pregnancy prior to administration of the second treatment (b) (4) test trilayer tablets). One subject, Subject 131, did not complete the final visit and was discontinued from the study due to being lost to follow-up. Three subjects were excluded from individual treatment summary statistics and statistical analysis.



All 40 subjects who were enrolled in the study also received at least 1 formulation. However, only 39 subjects had evaluable PK parameters and were included in the PK population. Subject 104 was discontinued from the study due to an AE on Day 1 of Period 1 following administration of the (b) (4) reference trilayer tablets, but prior to collection of sufficient blood samples and thus was not included in the PK population. Data from Subject 104 are listed in the concentration and PK parameter tables and individual subject figures, but were excluded from summary statistics, mean figures, and statistical analyses due to insufficient parameter characterization. Data from 4 additional subjects were either not collected or excluded from certain individual treatment PK summary statistics and/or statistical analysis for the following reasons: Subjects 106, 117, and 125 vomited within a specified time frame following dosing, and Subject 120 did not receive the specified treatment prior to discontinuing from the study.

Pharmacokinetic Results:

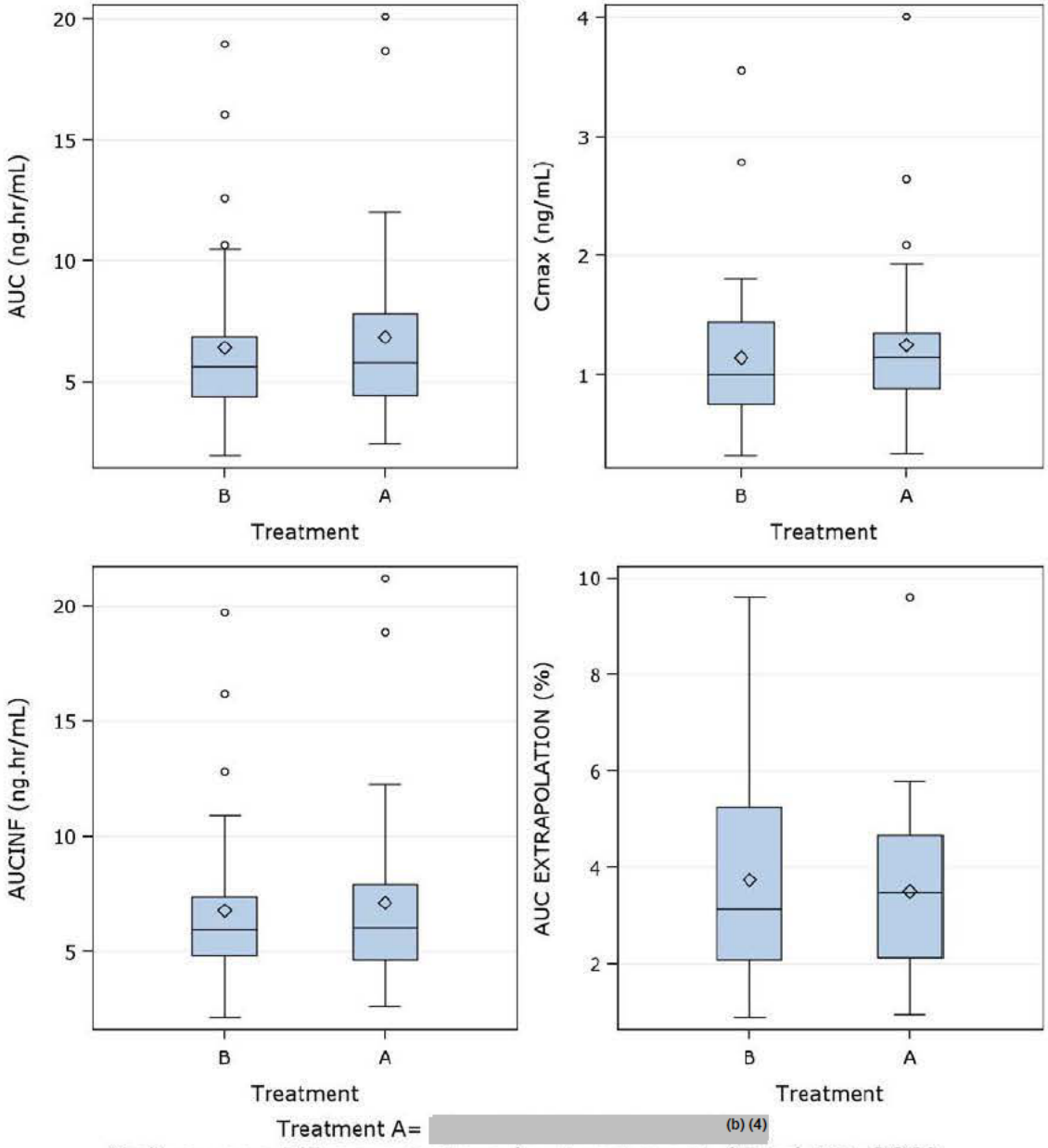
The concentration-time profiles of all analytes by treatment are shown in Figure below:



(b) (4)

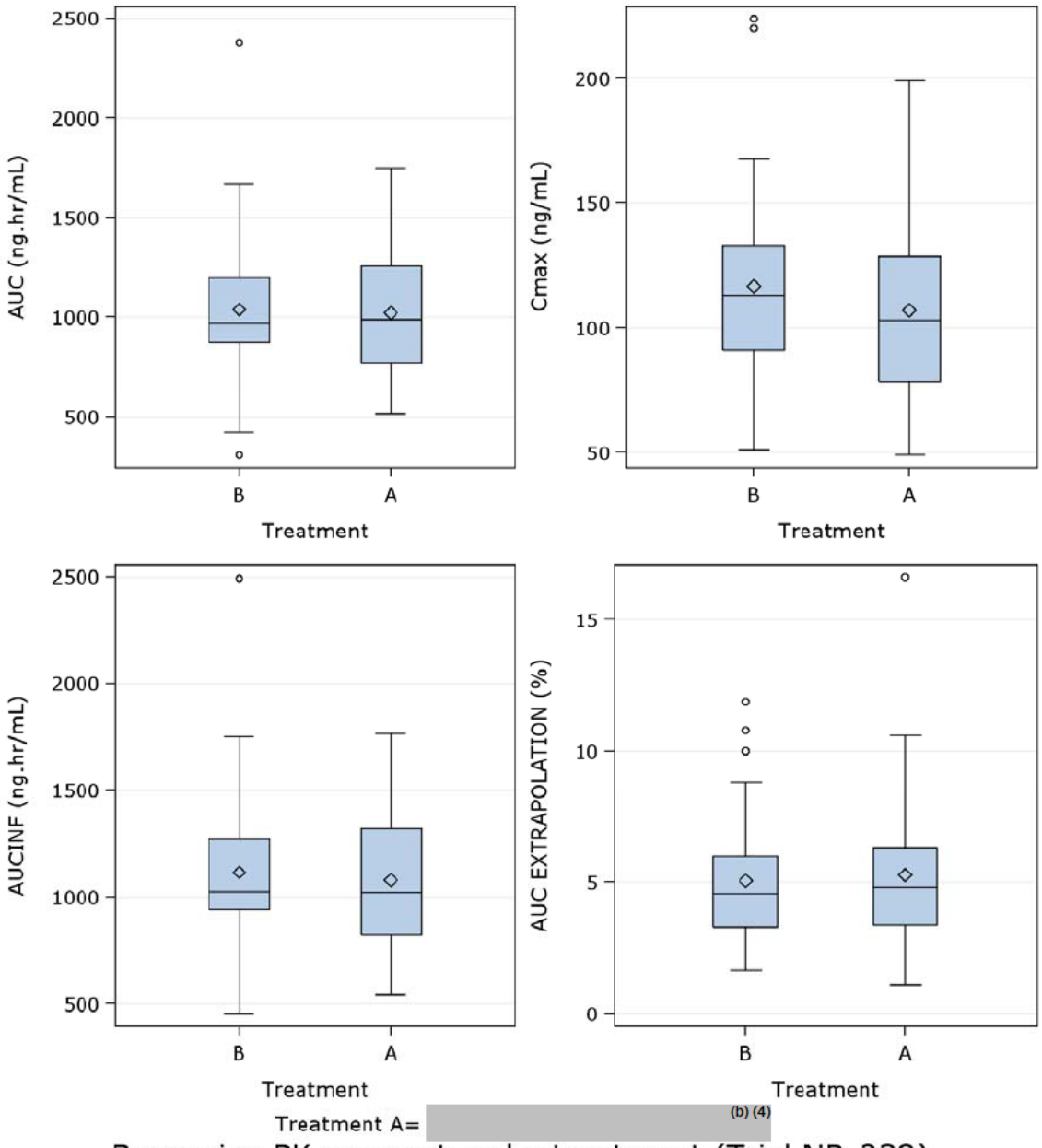
Mean(±)SE Concentration-time plots by treatment (Trial NB-229)

The distribution of PK parameters by treatment [redacted] (b) (4) for naltrexone and bupropion is summarized in the figures below:



Treatment A= [redacted] (b) (4)

Naltrexone PK parameters by treatment (Trial NB-229)



Bupropion PK parameters by treatment (Trial NB-229)

The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both naltrexone and bupropion.

The statistical comparison of PK parameters of naltrexone and bupropion are given in the following tables:

Table 1 Statistical comparison for naltrexone PK parameters [redacted]

Pharmacokinetic Parameter	N	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Interval
		Nal SR/Bup SR [redacted]	Nal SR/Bup SR [redacted]		
C_{max} (ng/mL)	35	1.129	1.030	109.52	102.74 - 116.76
AUC_{0-t} (ng*hr/mL)	35	6.074	6.030	100.73	96.25 – 105.42
$AUC_{0-\infty}$ (ng*hr/mL)	33	6.422	6.279	102.28	98.11 - 106.63

Nal SR/Bup SR [redacted] Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Test, Treatment B)
Nal SR/Bup SR [redacted] Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)
Subject 104 was excluded from both periods due to dropping from study.
Subject 106 Period 1 and Subject 117 Period 1 Treatment B were excluded due to vomiting.
Subject 120 Period 2 Treatment A was excluded due to not completing the study and never received Treatment A.
Subject 125 Period 1 Treatment A was excluded due to vomiting
N represents all subjects in the analysis including those with partial treatment due to discontinuation or vomiting.

Reviewer's Analysis with all subjects:

Statistical Comparison of Naltrexone PK Parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
[redacted]		AUC(0-inf)	ng.hr/mL	102.17	97.78 - 106.75
		AUC(0-t)	ng.hr/mL	102.94	99.12 - 106.9
		Cmax	ng/mL	108.7	101.93 - 115.92

Table 2 Statistical comparison for bupropion PK parameters [redacted]

Pharmacokinetic Parameter	N	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Interval
		Nal SR/Bup SR [redacted]	Nal SR/Bup SR [redacted]		
C_{max} (ng/mL)	35	102.496	114.017	89.90	84.45 – 95.69
AUC_{0-t} (ng*hr/mL)	35	974.857	1025.820	95.03	91.35 – 98.86
$AUC_{0-\infty}$ (ng*hr/mL)	34	1029.008	1082.104	95.09	91.34 – 99.00

Nal SR/Bup SR [redacted] Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Test, Treatment B)
Nal SR/Bup SR [redacted] Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)
Subject 104 was excluded from both periods due to dropping from study.
Subject 106 Period 1 and Subject 117 Period 1 Treatment B were excluded due to vomiting.
Subject 120 Period 2 Treatment A was excluded due to not completing the study and never received Treatment A.
Subject 125 Period 1 Treatment A was excluded due to vomiting
N represents all subjects in the analysis including those with partial treatment due to discontinuation or vomiting.

Reviewer's Analysis with all subjects:

Statistical Comparison of Bupropion PK Parameters

Test	Ref	PK Parameter	Units	Ratio(%)	90% CI
(b) (4)		AUC(0-inf)	ng.hr/mL	95.08	91.01 - 99.32
		AUC(0-t)	ng.hr/mL	95.29	91.31 - 99.45
		Cmax	ng/mL	89	83.49 - 94.87

Reviewer's Conclusions:

- These results show that the (b) (4) and (b) (4) naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets were bioequivalent. The 90% CI of the ratios of LS means derived from the analyses on the ln-transformed pharmacokinetic parameters Cmax, AUC0-t, and AUC0-inf for naltrexone and bupropion in plasma were within the 80 - 125% acceptance range required for the conclusion of bioequivalence between the treatments. These results were not affected by inclusion of all subjects.

1.1.5 DDI Study (NB-232)

Preface to the DDI Evaluation: Sponsor's DDI evaluation, as discussed by study for Study NB-232 and later for NB-233 and NB-234, was focused primarily on the effect of co-administration of various drugs (atorvastatin, valsartan, glyburide, metoprolol, lisinopril) on NB pharmacokinetics. These drugs were selected as general representative drugs from antihyperlipidemic, anti-hypertensive, anti-diabetic, which are likely to be co-administered in obese patient population with one or more co-morbid conditions. As secondary objective, sponsor also evaluated effect of Contrave on PK of these drugs by collecting the PK data for the co-administered drugs and comparing it to the historical data available in literature, FDA reviews or product labels. Agency did not agree on the originally proposed (b) (4) and later informed the sponsor that cross-study comparison will only be good for initial signal detection.

The study NB-232 was designed with multiple assessments, which include effects of single dose of atorvastatin (80 mg) or valsartan (360 mg) on the single dose plasma PK of 2 naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets (when given alone and when co-administered with these drugs) in healthy adult subjects. In addition, the effects of naltrexone (16 mg total) and bupropion (180 mg total) on the single dose plasma PK of atorvastatin or valsartan was estimated based on comparison to any previously published or reported results of these drugs when given alone as single-dose. Atorvastatin dose range is from 10 to 80 mg once daily (Lipitor®). The recommended start dose is 10 or 20 mg once daily. Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily. Valsartan (Diovan) is available as 40, 80, 160, and 320 mg scored tablets and dose range for adult hypertension is 80-320 mg once daily. The highest dose was evaluated for both atorvastatin and valsartan to maximize the potential for a PK interaction with naltrexone and/or bupropion (and their metabolites) to be detected.

The study design is as follows:

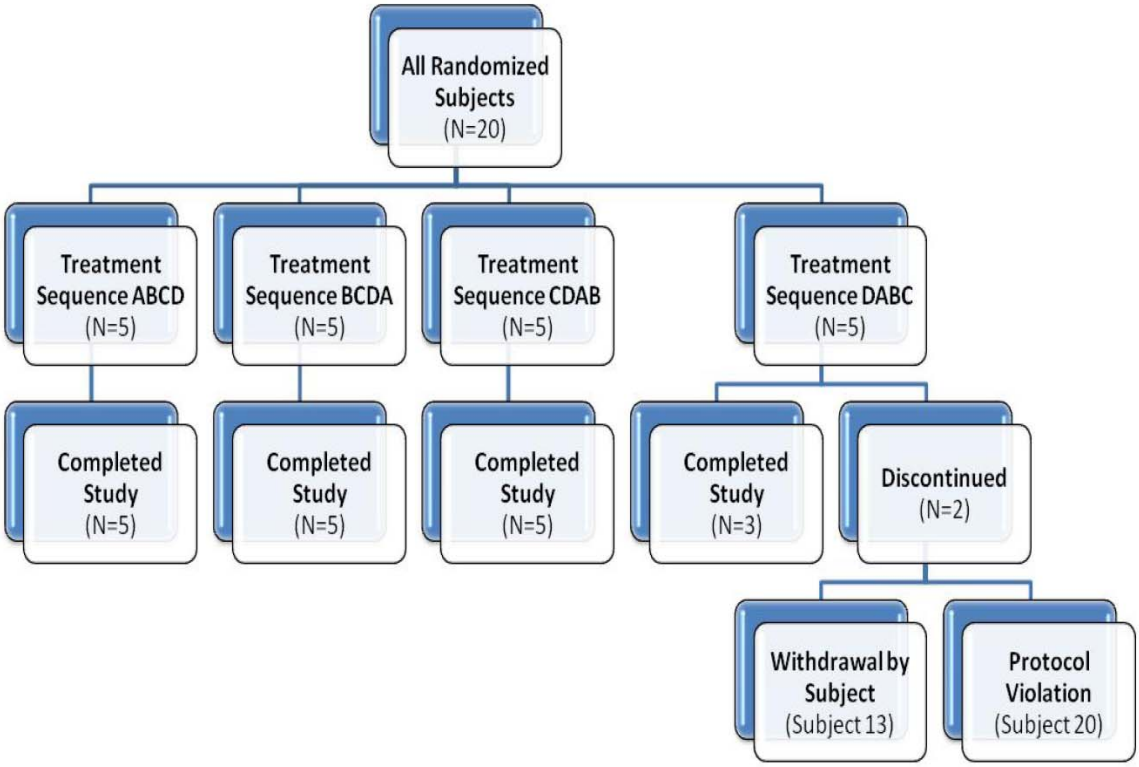
Title:	A Phase 1, Open-Label, Randomized, Single-Dose, Four-Way Crossover Study to Assess the Effects of Atorvastatin or Valsartan on the Pharmacokinetics of Naltrexone Sustained Release (SR)/Bupropion SR and to Determine the Relative Bioavailability of Two Different Strengths of Naltrexone SR/Bupropion SR Trilayer Tablets in Healthy Adult Subjects
Objectives:	**Primary:** 1. To assess the effects of single dose atorvastatin (80 mg) or valsartan (320 mg) on the single dose plasma pharmacokinetics (PK) of 2 naltrexone SR 8 mg sustained release (SR)/bupropion 90 mg combination trilayer tablets in healthy adults. 2. To assess the relative bioavailability of naltrexone SR 4 mg/bupropion SR 90 mg versus naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablet. **Secondary:** To compare the single dose plasma PK of atorvastatin and valsartan (given in combination with naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets) to previously published or reported results of these individual agents when given as monotherapy.
Study Design	The 4 study treatments (A, B, C, and D) were as follows: A = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets (Reference) B = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets co-

	administered with 1 atorvastatin 80 mg tablet (Test 1) C = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets co-administered with 1 valsartan 320 mg tablet (Test 2) D = Two naltrexone SR 4 mg/bupropion SR 90 mg Trilayer Tablets (Test 3) A total of 20 subjects were randomized to 4 treatment sequences (5 subjects per sequence. Prior to the start of the study, each subject was randomly assigned to 1 of 3 treatment sequences according to a Latin square design. The treatment sequence for each subject included all 4 treatments. Subjects received a single oral dose of each treatment on Day 1 of each treatment period, with a minimum 14-day washout period between dosing days. Treatments A and B were given under fasted conditions (at least a 10-hour fast).
Study Population	N= 20 Healthy subjects, Gender: 16 M and 4F, Age: 39 (20-56) yr Weight: 90.5 (69-123) kg, BMI: 30 (20-39)
Test Product	Two investigational naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets, Lot # C8B0367 (manufactured by (b) (4) co-administered with 1 atorvastatin 80 mg tablet, Lot #11738VB (Lipitor ®; Pfizer Inc.) given as a single oral dose (Test 1); Two investigational naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets, Lot # C8B0367 (manufactured by (b) (4) co-administered with 1 valsartan 320 mg tablet, Lot #F0479 (Diovan ; Novartis Pharmaceuticals Corporation) given as a single oral dose (Test 2); Two investigational naltrexone SR 4 mg/bupropion SR 90 mg trilayer tablets, Lot # C7K0321 (manufactured by (b) (4) given as a single oral dose (Test 3).
Reference Products	2 investigational naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablet Lot # C8B0367 (manufactured by (b) (4) given as a single oral dose.
Sampling: Blood	Blood samples for determination of naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, erythrohydrobupropion, and atorvastatin, o-hydroxy-atorvastatin, p-hydroxy-atorvastatin, and valsartan, plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (baseline), and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 120 hours postdose. Naltrexone elimination half-life (t1/2) is approximately 4 hr, bupropion has a t1/2 of 21 hr, atorvastatin has a t1/2 of ~20 hr, valsartan has t1/2 of 15 hr; thus, a 120-hr plasma concentration versus time profiling appears to be adequate for all analytes.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞,Cmax, Tmax, Kel, t1/2
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
2	B	C	D	A
3	C	D	A	B
4	D	A	B	C

Protocol Deviations:
There were no protocol deviations. Subject 20 was discontinued due to non-compliance with the study schedule.

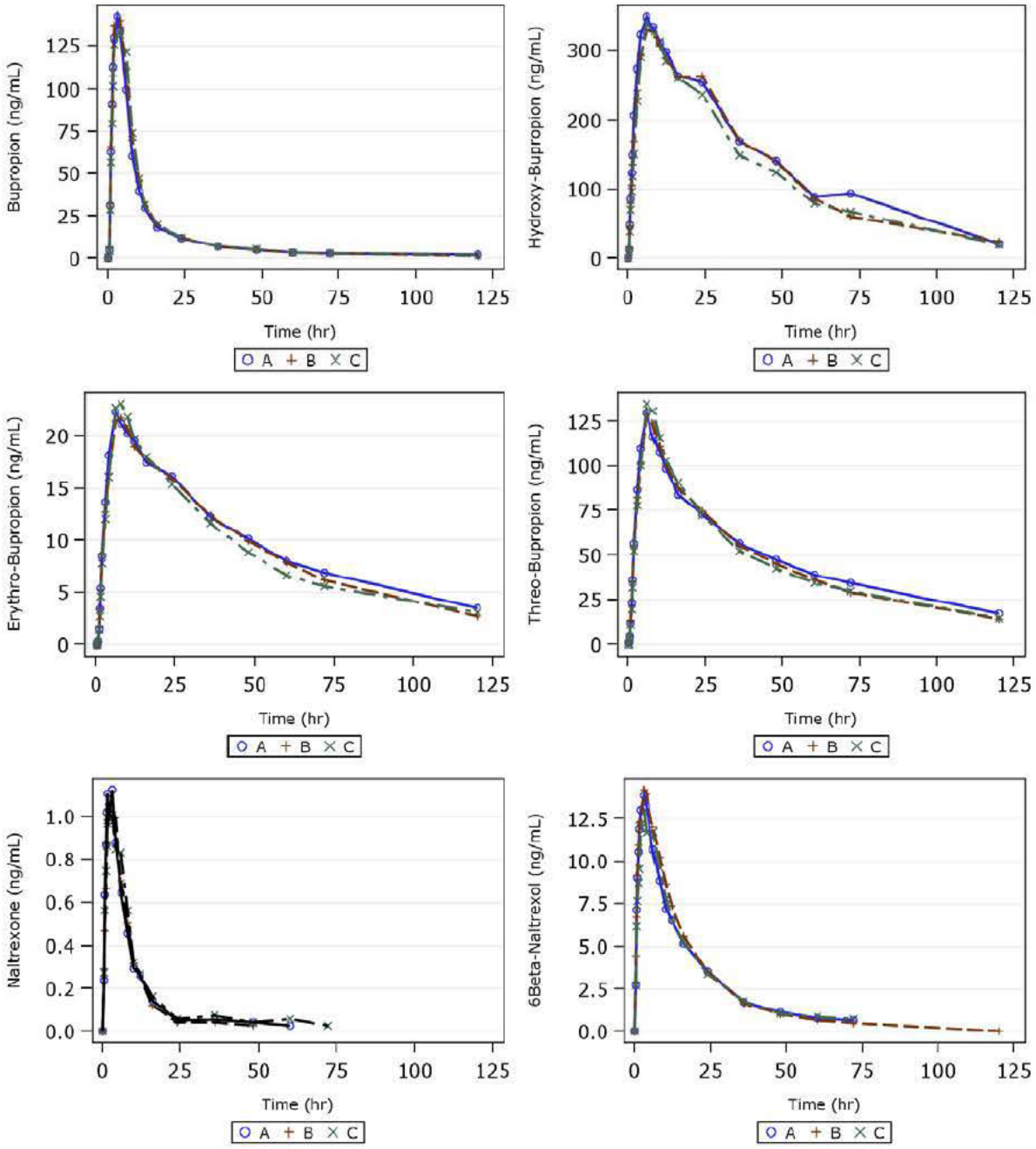
Subject Disposition and Data Sets Analyzed:



All 20 subjects who enrolled in the study received at least 1 of the 4 treatments and were included in the PK population. Data from 4 subjects were either not collected or excluded from certain individual treatment PK summary statistics and/or statistical analysis for the following reasons: did not receive the specified treatment prior to discontinuing from the study, vomited within a specified time frame following dosing.

Pharmacokinetic Results:

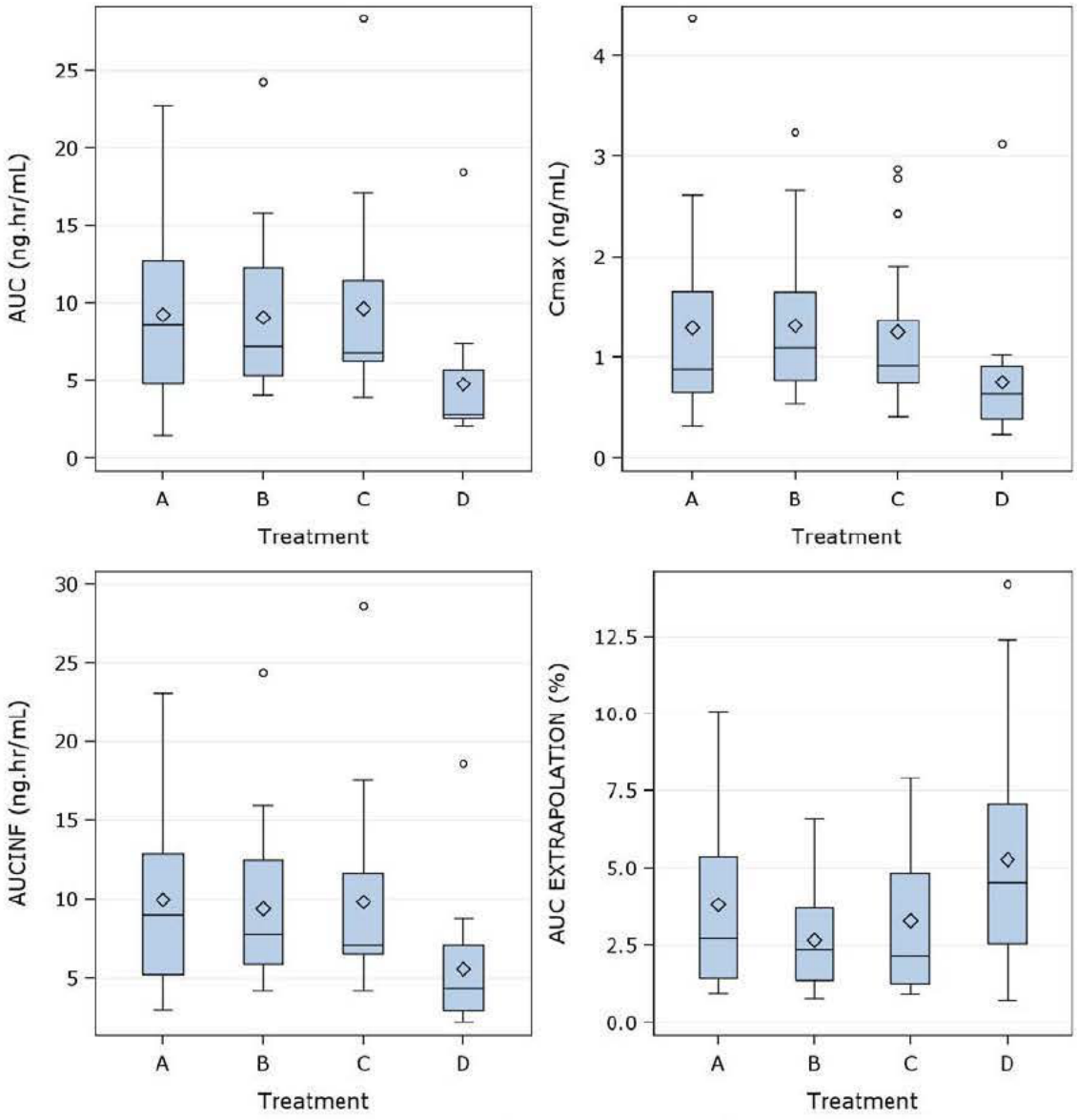
The concentration-time profiles of all analytes by treatment are shown in Figure below:



A = 2 x NB 8/90, B = 2 x NB 8/90 with Atorvastatin, C = 2 x NB 8/90 with Valsartan
Mean Concentration-time Plots by Treatment (Trial NB-232)

The distribution of PK parameters by treatment for naltrexone and bupropion are summarized in the figures below:

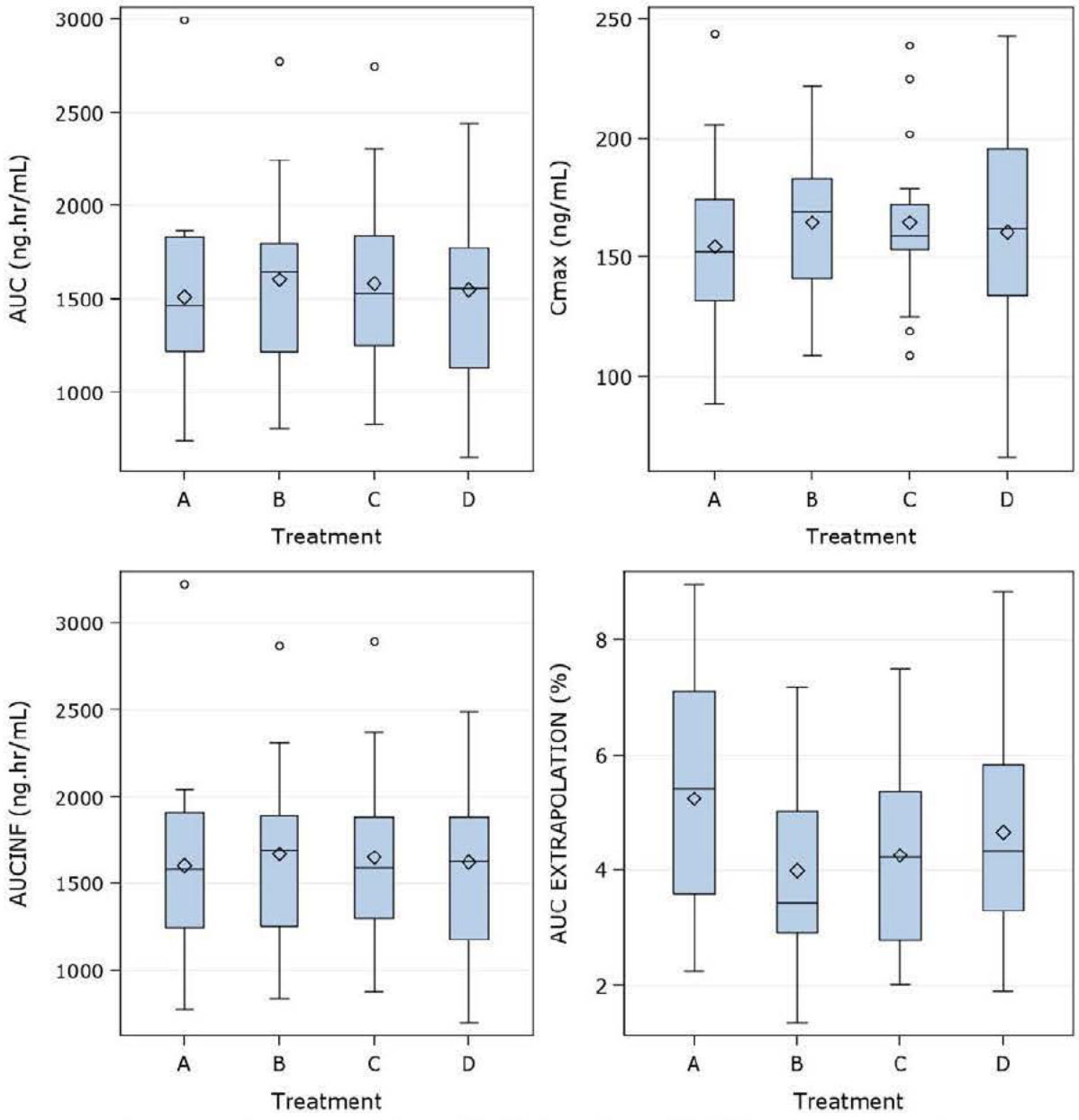
Naltrexone:



Treatment Description: A = 2xNB 8/90 mg, B = 2xNB 8/90 mg + Atorvastatin
Treatment Description: C = 2xNB 8/90 mg + Valsartan, D = 2xNB 4/90 mg

Naltrexone PK parameters by treatment (Trial NB-232)

Bupropion:



Treatment Description: A = 2xNB 8/90 mg, B = 2xNB 8/90 mg + Atorvastatin
Treatment Description: C = 2xNB 8/90 mg + Valsartan, D = 2xNB 4/90 mg

Bupropion PK parameters by treatment (Trial NB-232)

The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both naltrexone and bupropion.

The geometric mean ratios and 90% CIs for treatment comparisons for naltrexone, 6b-naltrexol, bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion (PAWC not presented) are provided in the tables below:

Table 1 Statistical comparison for naltrexone PK parameter (NB+Atorvastatin versus NB Alone)

		Evaluable PK Population (N=19)*			PK Population (N=20)
Plasma Analyte	PK Parameter	Nal SR/Bup SR	Nal SR/Bup SR + Ator	%MR (90% CI)‡	%MR (90% CI)‡
Naltrexone	C_{max} (ng/mL)	1.37 ± 0.943 (18)	1.34 ± 0.704 (19)	104.83 (90.85 - 120.97)	89.53 (70.15 - 114.27)
	T_{max} (hr)	1.76 (0.75, 6.00) (18)	2.00 (1.00, 5.99) (19)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	4.94 ± 1.60 (16)	4.05 ± 1.01 (19)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	9.62 ± 5.66 (18)	9.25 ± 5.13 (19)	98.22 (88.09 - 109.52)	82.69 (64.63 - 105.79)
	$AUC_{0-\infty}$ (ng*hr/mL)	10.55 ± 5.76 (16)	9.46 ± 5.13 (19)	94.74 (85.32 - 105.19)	96.90 (87.41 - 107.43)
6-Beta Naltrexol	C_{max} (ng/mL)	15.8 ± 4.46 (18)	16.6 ± 4.06 (19)	105.64 (96.69 - 115.42)	106.75 (97.28 - 117.14)
	T_{max} (hr)	2.50 (0.75, 6.00) (18)	2.00 (1.00, 5.99) (19)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	14.38 ± 2.94 (18)	15.36 ± 3.70 (19)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	243.27 ± 55.81 (18)	259.11 ± 55.52 (19)	106.66 (102.38- 111.12)	109.99 (103.09 - 117.35)
	$AUC_{0-\infty}$ (ng*hr/mL)	257.85 ± 57.52 (18)	274.31 ± 55.31 (19)	106.68 (103.18 - 110.30)	109.63 (103.65 - 115.96)

*Subject 20 was excluded from the PK analysis and the 2-hour time point concentrations were set to missing for Subject No. 7 (Treatment A) and Subject Nos. 4, 14 and 17 (Treatment D).
C_{max}, $t_{½}$, AUC_{0-t} and $AUC_{0-\infty}$ are presented as means ± SD (n), whereas T_{max} is presented as Median (Minimum, Maximum) (n)
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Nal SR/Bup SR + Ator = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Atorvastatin 80 mg Tablet (Test 1, Treatment B)
Subject 3, Period 2 Treatment A, was excluded from summary and statistical analyses due to vomiting.

Table 2 Statistical comparison for naltrexone PK parameter (NB+Valsartan versus NB Alone)

		Evaluable PK Population (N=19)*			PK Population (N=20)
Plasma Analyte	PK Parameter	Nal SR/Bup SR	Nal SR/Bup SR + Val	%MR (90% CI)‡	%MR (90% CI)‡
Naltrexone	C_{max} (ng/mL)	1.37 ± 0.943 (18)	1.27 ± 0.743 (18)	93.39 (80.68 - 108.10)	87.96 (68.26 - 113.35)
	T_{max} (hr)	1.76 (0.75, 6.00) (18)	2.00 (0.50, 6.05) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	4.94 ± 1.60 (16)	4.75 ± 1.46 (18)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	9.62 ± 5.66 (18)	9.89 ± 5.92 (18)	101.30 (90.63 - 113.22)	97.73 (75.64 - 126.27)
	$AUC_{0-\infty}$ (ng*hr/mL)	10.55 ± 5.76 (16)	10.14 ± 5.91 (18)	98.58 (88.59 - 109.70)	100.73 (90.65 - 111.92)
6-Beta Naltrexol	C_{max} (ng/mL)	15.8 ± 4.46 (18)	15.4 ± 4.39 (18)	95.67 (87.39 - 104.73)	96.53 (87.78 - 106.14)
	T_{max} (hr)	2.50 (0.75, 6.00) (18)	3.00 (0.75, 6.05) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	14.38 ± 2.94 (18)	14.97 ± 3.55 (18)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	243.27 ± 55.81 (18)	227.95 ± 47.30 (18)	92.64 (88.84 - 96.60)	95.58 (89.45 - 102.13)
	$AUC_{0-\infty}$ (ng*hr/mL)	257.85 ± 57.52 (18)	245.67 ± 48.98 (18)	94.19 (91.02 - 97.47)	96.99 (91.57 - 102.73)

*Subject 20 was excluded from the PK analysis and the 2-hour time point concentrations were set to missing for Subject No. 7 (Treatment A) and Subject Nos. 4, 14 and 17 (Treatment D).
C_{max}, $t_{½}$, AUC_{0-t} and $AUC_{0-\infty}$ are presented as means ± SD (n), whereas T_{max} is presented as Median (Minimum, Maximum) (n)
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Nal SR/Bup SR + Val = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Valsartan 320 mg Tablet (Test 2, Treatment C)
Subject 3, Period 2 Treatment A, was excluded from summary and statistical analyses due to vomiting.

Table 3 Statistical comparison for bupropion PK parameter (NB+Valsartan versus NB Alone)

Evaluable PK Population (N=19)*					PK Population (N=20)
Plasma Analyte	PK Parameter	Nal SR/Bup SR	Nal SR/Bup SR + Ator	%MR (90% CI)‡	%MR (90% CI)‡
Bupropion	C_{max} (ng/mL)	157 ± 35.7 (18)	164 ± 29.1 (19)	104.85 (95.64 - 114.96)	86.59 (67.41 - 111.23)
	T_{max} (hr)	3.00 (1.25, 4.00) (18)	2.10 (1.50, 5.99) (19)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	24.74 ± 6.74 (18)	25.33 ± 8.34 (19)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	1523.25 ± 500.58 (18)	1603.55 ± 467.17 (19)	105.25 (99.67 - 111.15)	91.25 (75.19 - 110.73)
	$AUC_{0-\infty}$ (ng*hr/mL)	1613.41 ± 549.55 (18)	1670.35 ± 484.67 (19)	103.88 (98.45 - 109.60)	105.62 (99.53 - 112.08)
Hydroxybupropion	C_{max} (ng/mL)	365 ± 172 (18)	351 ± 123 (19)	96.77 (89.80 - 104.28)	76.87 (56.72 - 104.18)
	T_{max} (hr)	6.01 (3.99, 72.00) (18)	6.00 (4.00, 11.99) (19)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	29.83 ± 5.97 (16)	28.38 ± 6.25 (17)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	17563.61 ± 8906.10 (18)	15353.69 ± 5921.43 (19)	89.96 (82.93 - 97.59)	68.83 (47.88 - 98.96)
	$AUC_{0-\infty}$ (ng*hr/mL)	19087.41 ± 9761.76 (16)	15392.26 ± 6019.46 (17)	96.26 (88.61 -104.56)	71.41 (49.96 - 102.08)
Threohydrobupropion	C_{max} (ng/mL)	137 ± 57.6 (18)	136 ± 46.9 (19)	99.56 (93.76 - 105.72)	101.43 (94.97 - 108.32)
	T_{max} (hr)	6.00 (3.99, 8.01) (18)	6.00 (5.98, 8.00) (19)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	45.06 ± 9.98 (13)	47.62 ± 7.66 (16)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	6096.45 ± 4163.75 (18)	5833.65 ± 3828.94 (19)	96.93 (91.85 - 102.29)	100.11 (92.74 - 108.06)
	$AUC_{0-\infty}$ (ng*hr/mL)	7715.50 ± 6582.76 (13)	7031.08 ± 4463.37 (16)	101.90 (94.63 - 109.72)	106.00 (95.67 - 117.43)
Erythrohydrobupropion	C_{max} (ng/mL)	23.5 ± 6.42 (18)	23.7 ± 6.23 (19)	99.73 (95.11 - 104.58)	102.83 (96.11 - 110.02)
	T_{max} (hr)	6.01 (5.99, 12.00) (18)	8.00 (5.98, 16.00) (19)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	32.92 ± 8.93 (16)	31.69 ± 7.63 (18)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	1154.17 ± 648.99 (18)	1155.09 ± 654.37 (19)	100.41 (94.67 - 106.49)	104.03 (95.78 - 113.00)
	$AUC_{0-\infty}$ (ng*hr/mL)	1264.53 ± 702.59 (16)	1305.06 ± 792.81 (18)	98.64 (92.96 - 104.67)	103.09 (94.62 - 112.32)

*Subject 20 was excluded from the PK analysis and the 2-hour time point concentrations were set to missing for Subject No. 7 (Treatment A) and Subject Nos. 4, 14 and 17 (Treatment D).
C_{max}, $t_{½}$, AUC_{0-t} and $AUC_{0-\infty}$ are presented as means ± SD (n), whereas T_{max} is presented as Median (Minimum, Maximum) (n)
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Nal SR/Bup SR + Val = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Valsartan 320 mg Tablet (Test 2, Treatment C)
Subject 3, Period 2 Treatment A, was excluded from 90% CI and % MR calculation due to vomiting.

Table 4 Statistical comparison for bupropion PK parameter (NB+Valsartan versus NB Alone)

Evaluable PK Population (N=19)*					Evaluable PK Population (N=20)
Plasma Analyte	PK Parameter	Nal SR/Bup SR	Nal SR/Bup SR + Val	%MR (90% CI)‡	%MR (90% CI)‡
Bupropion	C_{max} (ng/mL)	157 ± 35.7 (18)	165 ± 32.6 (18)	103.68 (94.38 - 113.89)	101.85 (78.63 - 131.93)
	T_{max} (hr)	3.00 (1.25, 4.00) (18)	3.00 (1.49, 6.00) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	24.74 ± 6.74 (18)	26.74 ± 8.27 (18)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	1523.25 ± 500.58 (18)	1581.20 ± 494.70 (18)	101.12 (95.64 - 106.92)	98.89 (80.87 - 120.93)
	$AUC_{0-\infty}$ (ng*hr/mL)	1613.41 ± 549.55 (18)	1649.44 ± 510.89 (18)	100.08 (94.74 - 105.72)	101.77 (95.77 - 108.14)
Hydroxybupropion	C_{max} (ng/mL)	365 ± 172 (18)	351 ± 125 (18)	96.09 (89.03 - 103.72)	92.67 (67.59 - 127.06)
	T_{max} (hr)	6.01 (3.99, 72.00) (18)	6.00 (4.00, 15.97) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	29.83 ± 5.97 (16)	28.23 ± 6.80 (18)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	17563.61 ± 8906.10 (18)	14425.43 ± 5966.95 (18)	82.61 (76.02 - 89.78)	79.81 (54.73 - 116.38)
	$AUC_{0-\infty}$ (ng*hr/mL)	19087.41 ± 9761.76 (16)	15366.31 ± 6817.73 (18)	85.60 (78.98 - 92.77)	81.36 (57.05 - 116.04)
Threohydrobupropion	C_{max} (ng/mL)	137 ± 57.6 (18)	140 ± 44.4 (18)	102.46 (96.36 – 108.94)	104.37 (97.59 - 111.63)
	T_{max} (hr)	6.00 (3.99, 8.01) (18)	6.00 (2.01, 8.02) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	45.06 ± 9.98 (13)	46.49 ± 9.48 (16)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	6096.45 ± 4163.75 (18)	5468.16 ± 3695.85 (18)	89.52 (84.73 - 94.58)	92.49 (85.54 - 100.01)
	$AUC_{0-\infty}$ (ng*hr/mL)	7715.50 ± 6582.76 (13)	5651.95 ± 2282.83 (16)	90.59(83.69 - 98.06)	94.69 (84.89 - 105.64)
Erythrohydrobupropion	C_{max} (ng/mL)	23.5 ± 6.42 (18)	24.0 ± 5.78 (18)	101.21 (96.42 - 106.24)	104.40 (97.43 - 111.87)
	T_{max} (hr)	6.01 (5.99, 12.00) (18)	7.00 (2.01, 10.00) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	32.92 ± 8.93 (16)	32.21 ± 9.50 (17)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	1154.17 ± 648.99 (18)	1011.37 ± 481.12 (18)	88.83 (83.65 - 94.33)	92.08 (84.61 - 100.21)
	$AUC_{0-\infty}$ (ng*hr/mL)	1264.53 ± 702.59 (16)	1056.73 ± 395.38 (17)	87.98 (82.80 - 93.47)	91.87 (84.15 - 100.29)

*Subject 20 was excluded from the PK analysis and the 2-hour time point concentrations were set to missing for Subject No. 7 (Treatment A) and Subject Nos. 4, 14 and 17 (Treatment D).
C_{max}, $t_{½}$, AUC_{0-t} and $AUC_{0-\infty}$ are presented as means ± SD (n), whereas T_{max} is presented as Median (Minimum, Maximum) (n)
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Nal SR/Bup SR + Val = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Valsartan 320 mg Tablet (Test 2, Treatment C)
Subject 3, Period 2 Treatment A, was excluded from 90% CI and % MR calculation due to vomiting.

Table 5 Comparison for Atorvastatin PK parameters (NB+Atorvastatin) with published information

	Analyte	AUC_{∞} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NB-232[a] Lipitor®, 80 mg	ATV	161 (43%) (78 – 336)	31.0 (43%) (11 – 66)	0.95 (97%) (0.43 - 3.99)	7.19 (58%) (3.51 – 18.8)
	o-ATV	169 (57%) (54 – 510)	18.8 (50%) 6.86 – 36.0)	2.17 (100%) (0.74 -10.0)	9.29 (59%) (3.58 – 25.2)
	p-ATV	42 (112%) (14 – 167)	1.50 (76%) (0.62– 5.33)	9.06 (36%) (0.74 -12.0)	14.2 (54%) (6.16 – 26.8)
Mendoza L et al. (2006) Lipitor®, 40 mg	ATV	57.7	14.5	0.69 (55%)	9.07 (30%)
	o-ATV	69.6	10.5	1.27 (78%)	9.11 (21%)
(b) (4) data on file (80 mg)	ATV	148 (41%)	35 (55%)	1 (75%)	15 (45%)
	o-ATV	211 (43%)	32 (60%)	1.5 (70%)	16 (35%)
	p-ATV	29 (57%)	2 (100%)	6 (100%)	27 (50%)
Posvar EL et al. (1996) (80 mg)	ATV	335 (50 - 850)	33.1 (10 – 100)	2.8 (0.5 – 6)	19.2 (14.7 – 57.6)
	o-ATV	Not Available	Not Available	Not Available	Not Available

Table 6 Comparison for Valsartan PK parameters (NB+Valsartan) with published information

Study	AUC_{0-t} (ng*h/mL)	AUC_{∞} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
NB-232[a] (320 mg)	41615 (45%)	43867 (45%)	4600 (39%)	4.00 (1.3 – 8)	11.9 (73%)
FDA[b] (320 mg)	41050 (33%)	42683 (31%)	6162 (34%)	2.75 (1 – 4.37)	14.7 (65%)
Séchaud R et.al. (320 mg)	Not Available	42680	6162	2.75 (1 – 4.37)	Not Available
Schmidt EK et al. (160 mg)	Not Available	Not Available	2250 (48)	2.0 (2.0 – 3.0)	5.73 (15%)

[b]Data from FDA Clinical Pharmacology and Biopharmaceutics Review, Application Number 21-283 (Diovan tablets).
AUCs and $t_{1/2}$ are expressed as mean with or without CV whereas T_{max} is given as median (range).

Table 7 Comparison for naltrexone PK parameters (NB 2 x 4/90 mg versus NB 2 x 8/90 mg trilayer tablets)

Evaluable PK Population (N=19)*					PK Population (N=20)
Dose-Normalized Plasma Analyte	PK Parameter	Nal SR/Bup SR (8/90)	Nal SR/Bup SR (4/90)	%MR (90% CI)‡	%MR (90% CI)‡
Naltrexone	C_{max} (ng/mL/mg)	0.0853 ± 0.0589 (18)	0.0900 ± 0.0812 (18)	105.01 (85.53 - 128.94)	126.54 (100.72 - 158.97)
	T_{max} (hr)	1.76 (0.75, 6.00) (18)	1.26 (0.97, 12.00) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	4.94 ± 1.61 (16)	4.32 ± 0.93 (14)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL/mg)	0.60 ± 0.35 (18)	0.57 ± 0.49 (18)	89.76 (77.41 - 104.09)	99.06 (85.80 - 114.36)
	$AUC_{0-\infty}$ (ng*hr/mL/mg)	0.66 ± 0.36 (16)	0.66 ± 0.53 (14)	100.91 (82.67 - 123.19)	110.47 (94.86 - 128.66)
6-Beta Naltrexol	C_{max} (ng/mL/mg)	0.991 ± 0.280 (18)	0.999 ± 0.341 (18)	101.97 (90.02 - 115.50)	110.16 (98.59 - 123.08)
	T_{max} (hr)	2.50 (0.75, 6.00) (18)	2.00 (1.25, 6.00) (18)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	14.38 ± 2.94 (18)	13.16 ± 1.73 (17)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL/mg)	15.21 ± 3.49 (18)	13.15 ± 3.55 (18)	85.93 (81.04 - 91.12)	92.25 (83.57 - 101.84)
	$AUC_{0-\infty}$ (ng*hr/mL/mg)	16.12 ± 3.60 (18)	14.98 ± 3.61 (17)	91.55 (86.39 – 97.01)	100.27 (91.87 - 109.45)

*Subject 20 was excluded from the PK analysis and the 2-hour time point concentrations were set to missing for Subject No. 7 (Treatment A) and Subject Nos. 4, 14 and 17 (Treatment D).
C_{max}, $t_{½}$, AUC_{0-t} and $AUC_{0-\infty}$ are presented as means ± SD (n), whereas T_{max} is presented as Median (Minimum, Maximum) (n)
‡ = 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR (8/90) = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Nal SR/Bup SR (4/90) = Two Naltrexone SR 4 mg/Bupropion SR 90 mg Trilayer Tablets (Test 3, Treatment D)
Subject 3, Period 2 Treatment A, was excluded from summary and statistical analyses due to vomiting.
Subject 7, Period 1 Treatment D, was excluded from summary and statistical analyses due to vomiting.

Table 7 Comparison for bupropion PK parameters (NB 2 x 4/90 mg versus NB 2 x 8/90 mg trilayer tablets)

Plasma Analyte	PK Parameter	%MR (90% CI)‡	PK Population (N=20) %MR (90% CI)‡
Bupropion	C_{max} (ng/mL)	100.42 (91.42 - 110.31)	101.35 (78.61 - 130.66)
	T_{max} (hr)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	101.81 (96.29 - 107.64)	104.88 (86.13 - 127.71)
	$AUC_{0-\infty}$ (ng*hr/mL)	100.92 (95.53 - 106.61)	104.24 (98.25 - 110.60)
Hydroxybupropion	C_{max} (ng/mL)	106.08 (98.28 - 114.50)	110.71 (81.27 - 150.81)
	T_{max} (hr)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	92.22 (84.86 - 100.22)	98.22 (67.89 - 142.10)
	$AUC_{0-\infty}$ (ng*hr/mL)	96.39 (88.78 - 104.64)	99.56 (69.97 - 141.68)
Threohydrobupropion	C_{max} (ng/mL)	102.83 (96.71 - 109.33)	106.19 (99.45 - 113.39)
	T_{max} (hr)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	96.16 (91.02 - 101.60)	102.15 (94.65 - 110.24)
	$AUC_{0-\infty}$ (ng*hr/mL)	97.09 (89.78 - 104.99)	104.55 (94.11 - 116.15)
Erythrohydrobupropion	C_{max} (ng/mL)	104.36 (99.42 - 109.55)	110.06 (102.89 - 117.74)
	T_{max} (hr)	Not Applicable	Not Applicable
	$t_{1/2}$ (hr)	Not Applicable	Not Applicable
	AUC_{0-t} (ng*hr/mL)	99.20 (93.41 - 105.34)	105.82 (97.44 - 114.91)
	$AUC_{0-\infty}$ (ng*hr/mL)	97.86 (92.18 - 103.90)	105.17 (96.68 - 114.41)

Conclusions:

- Co-administration with single dose of either atorvastatin or valsartan did not effect the PK of single dose of naltrexone and bupropion in the naltrexone SR/bupropion SR trilayer combination. The % geometric mean ratios and the 90% CI of the naltrexone and bupropion PK parameters obtained from the evaluable PK population were within 80 - 125%.
- The comparison with literature data showed that co-administration of a single dose of 2 naltrexone SR 8 mg/bupropion SR 90 mg tablets in combination with 1 atorvastatin 80 mg tablet or with 1 valsartan 320 mg tablet did not point towards any effect on the PK exposure of atorvastatin or valsartan.
- No clinically significant difference in dose-adjusted AUC0-inf values between naltrexone SR 4 mg/bupropion SR 90 mg and naltrexone SR 8 mg/bupropion SR 90 mg alone (Reference) was detected. In addition, a less than 11% difference in plasma naltrexone AUC0-t and Cmax was observed between both treatments. Therefore, naltrexone exposures were approximately dose proportional between single doses of 8 and 16 mg in the naltrexone SR/bupropion SR combination. The PK parameters of bupropion were comparable between the two formulations.
- Single-dose administration of naltrexone SR 8 mg/bupropion SR 90 mg + atorvastatin, naltrexone SR 8 mg/bupropion SR 90 mg + valsartan, and naltrexone SR 4 mg/bupropion SR90 mg appeared to be generally safe and well tolerated by the healthy male and female subjects in this study.

Reviewer's Comments: Overall, sponsor's conclusions from this study are reasonable and acceptable with some notable exceptions. Comparison of atorvastatin PK data with the literature was limited to Cmax for direct comparison of the 80 mg dose as there are notable differences in the AUCs, and half-life between sponsor's values and those reported by Posavar et al 1996. In absence of the comparison of bioanalytical methods, the reason cannot be determined. The valsartan data comparison does provide preliminary signal that a mutual interaction is unlikely.

1.1.6 DDI and High-Fat Food Effect Study (NB-233)

This study assessed the effects of a single dose of micronized glyburide (6 mg) on the single dose plasma PK of 2 naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets (when given alone and when co-administered with micronized glyburide) in healthy adult subjects. In addition, the effects of naltrexone (16 mg total) and bupropion (180 mg total) on the single dose plasma PK of micronized glyburide (6 mg) was estimated based on comparison to any previously published or reported results of this agent when given as single-dose monotherapy. Micronized glyburide is a commercially available marketed product in the US. The maximum suggested starting dose of micronized glyburide is 1.5 to 3 mg daily; however, a 6 mg single dose was evaluated in this study to better maximize the potential for a PK interaction with naltrexone and/or bupropion (and their active metabolites) to be detected.

In the Phase 3 trials with naltrexone SR/bupropion SR combination trilayer tablets, administration with meals is recommended to potentially minimize gastrointestinal (GI) intolerance (e.g., nausea) to treatment. According to the Wellbutrin® SR label, food increases the Cmax and AUC of bupropion by 11% and 17%, respectively. With respect to naltrexone, the effect of food on the PK of naltrexone has not been reported. Therefore, this study also included the evaluation of the effect of food (standard high-fat breakfast), compared to the fasted state (at least a 10-hour fast) on the single dose plasma PK of 2 naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets in healthy adult subjects.

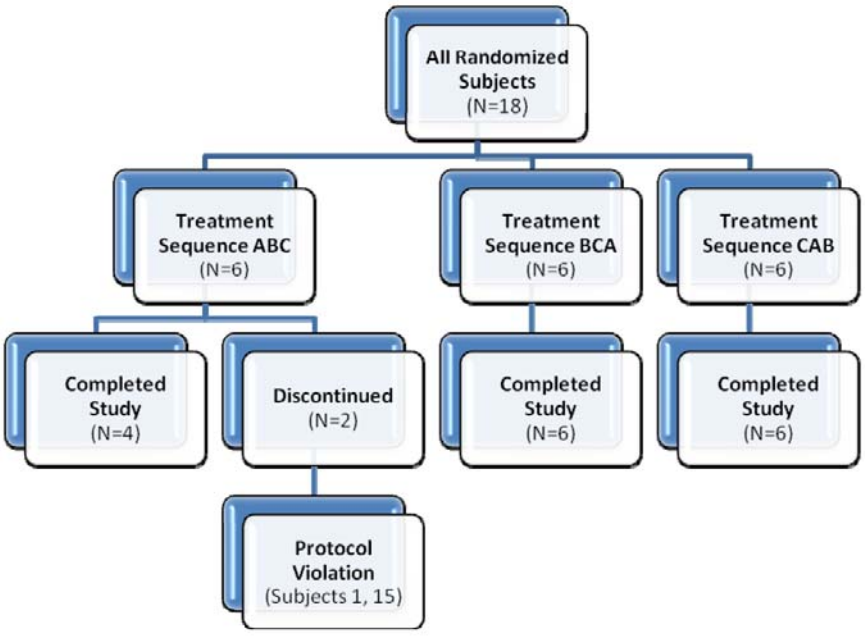
The study design is as follows:

Title:	A Phase 1, Open-Label, Randomized, Single-Dose, Three-Way Crossover Study to Assess the Effects of Micronized Glyburide or Food on the Plasma Pharmacokinetics of Naltrexone SR/Bupropion SR Combination Trilayer Tablets in Healthy Adult Subjects
Objectives:	**Primary:** 1. To assess the effects of single dose micronized glyburide (6 mg) on the single dose plasma pharmacokinetics (PK) of 2 naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets given under fasted conditions in healthy adult subjects. 2. To compare the effects of fasted and fed conditions on the plasma PK of 2 naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets in healthy adult subjects. **Secondary:** 1. To compare the single dose plasma PK of micronized glyburide (given in combination with naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets) to previously published or reported results of this drug when given as single-dose monotherapy. 2. To assess the safety and tolerability of single doses of the 3 evaluated treatments.
Study Design	This was a Phase 1, open-label, randomized, single-dose, 3-way crossover study to assess the effects of micronized glyburide (6 mg) or food on the plasma PK of naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets in healthy adult subjects. The 3 study treatments (A, B, and C) were as follows: A = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets given under fasted conditions (Reference, Nal SR/Bup SR, Fasted). B = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets co-

	administered with 1 micronized glyburide 6 mg tablet given under fasted conditions (Test 1, Nal SR/Bup SR + Gly). C = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets given under fed conditions (standard high-fat breakfast) (Test 2, Nal SR/Bup SR, Fed). Prior to the start of the study, each subject was randomly assigned to 1 of 3 treatment sequences according to a Latin square design. The treatment sequence for each subject included all 3 treatments: Treatment A (Reference), Treatment B (Test 1), and Treatment C (Test 2). Subjects received a single oral dose of each treatment on Day 1 of each treatment period, with a minimum 14-day washout period between dosing days. Treatments A and B were given under fasted conditions (at least a 10-hour fast). To minimize any possible hypoglycemic effects, Treatment B was taken orally with 240 mL of 20% glucose solution, with an additional 60 mL of this glucose solution given approximately every 15 minutes (starting 15 minutes postdose) until 15 minutes prior to the 4-hour postdose meal. Treatment C was given under fed conditions (subjects ingested a standard high-fat breakfast within 30 minutes before dosing). Treatments A and C were taken orally with 240 mL (8 ounces) of water.
Study Population	N= 18 Healthy subjects, Gender: 13 M and 14F, Age: 33 (19-60) yr Weight: 87.5 (53-135) kg, BMI: 30.1 (20-40)
Test Product	1) Two investigational naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets (manufactured by (b) (4)), Lot No.: C8B0367, co-administered with 1 micronized glyburide 6 mg tablet (Glynase®; Pharmacia and Upjohn Company), Lot No.: 08T4551A , given as a single oral dose under fasted conditions (Test 1). 2) Two investigational naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets (manufactured by (b) (4), Lot No.: C8B0367, given as a single oral dose under fed conditions (Test 2).
Reference Products	The reference treatment in this study was 2 investigational naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets (manufactured by (b) (4) Lot No.: C8B0367), given as a single oral dose under fasted conditions.
Sampling: Blood	Blood samples for determination of naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (baseline), and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 120 hours postdose. Naltrexone elimination half-life (t1/2) is approximately 4 hr, bupropion has a t1/2 of 21 hr and glyburide has a t1/2 of ~4 hr; thus, a 120-hr plasma concentration versus time profiling appears to be adequate for all analytes.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞,Cmax, Tmax, Kel, t1/2
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Protocol Deviations:
According to the protocol, subjects were restricted from consuming mustard from 48 hours prior to dosing until approximately 72 hours postdose as this food item may affect CYP activity. However, on Day 1 at the 4.5-hour time point, Subjects 5 and 12 consumed mustard with their lunch. Moreover, according to the protocol, subjects dosed with Treatment C (Nal SR/Bup SR, Fed) were to have consumed a high-fat, high-calorie breakfast within 30 minutes of dosing. However, on Day 1 of Period 3, Subjects 2, 4, 9, 11, 13, and 18 dosed with Treatment C (Nal SR/Bup SR, Fed) started their breakfast approximately 15 minutes early. These meal deviations were not expected to have an impact on the marked food effect observed in this study.

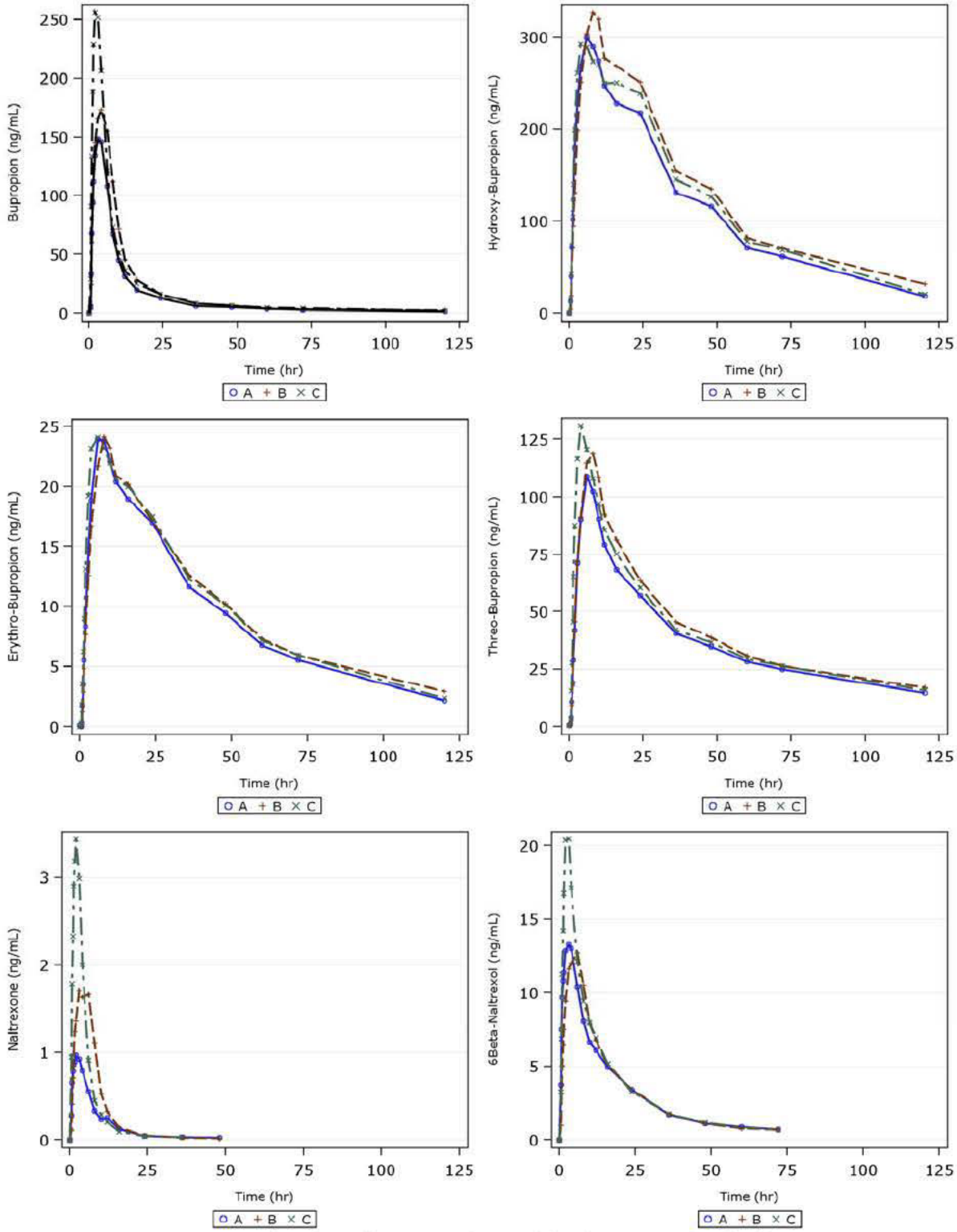
Subject Disposition and Data Sets Analyzed:



All 18 subjects who enrolled in the study received at least 1 of the 3 treatments and were included in the PK population. Data from 6 subjects were either not collected or excluded from certain individual treatment PK summary statistics and/or statistical analysis for the following reasons: did not receive the specified treatment prior to discontinuing from the study, vomited within a specified time frame following dosing, and/or had insufficient data to reliably calculate certain PK parameters.

Pharmacokinetic Results:

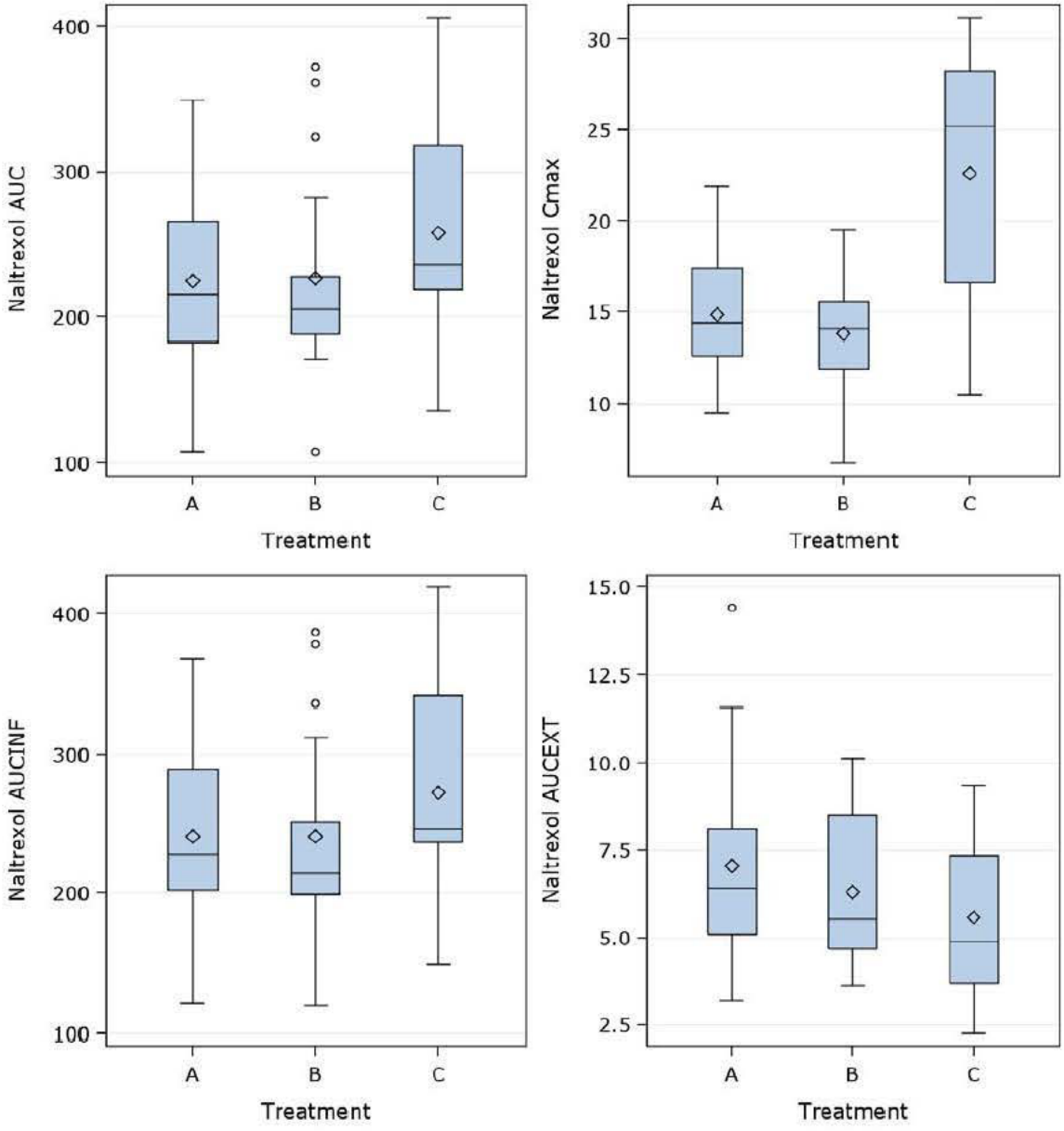
The concentration-time profiles of all analytes by treatment are shown in Figure below:



A = NB 8/90 (Fasted), B = NB 8/90 + Glyburide, C = NB 8/90 (Fed)
Mean(±)SE Concentration-time plots by treatment (Trial NB-233)

The distribution of PK parameters by treatment for naltrexone and bupropion are summarized in the figures below:

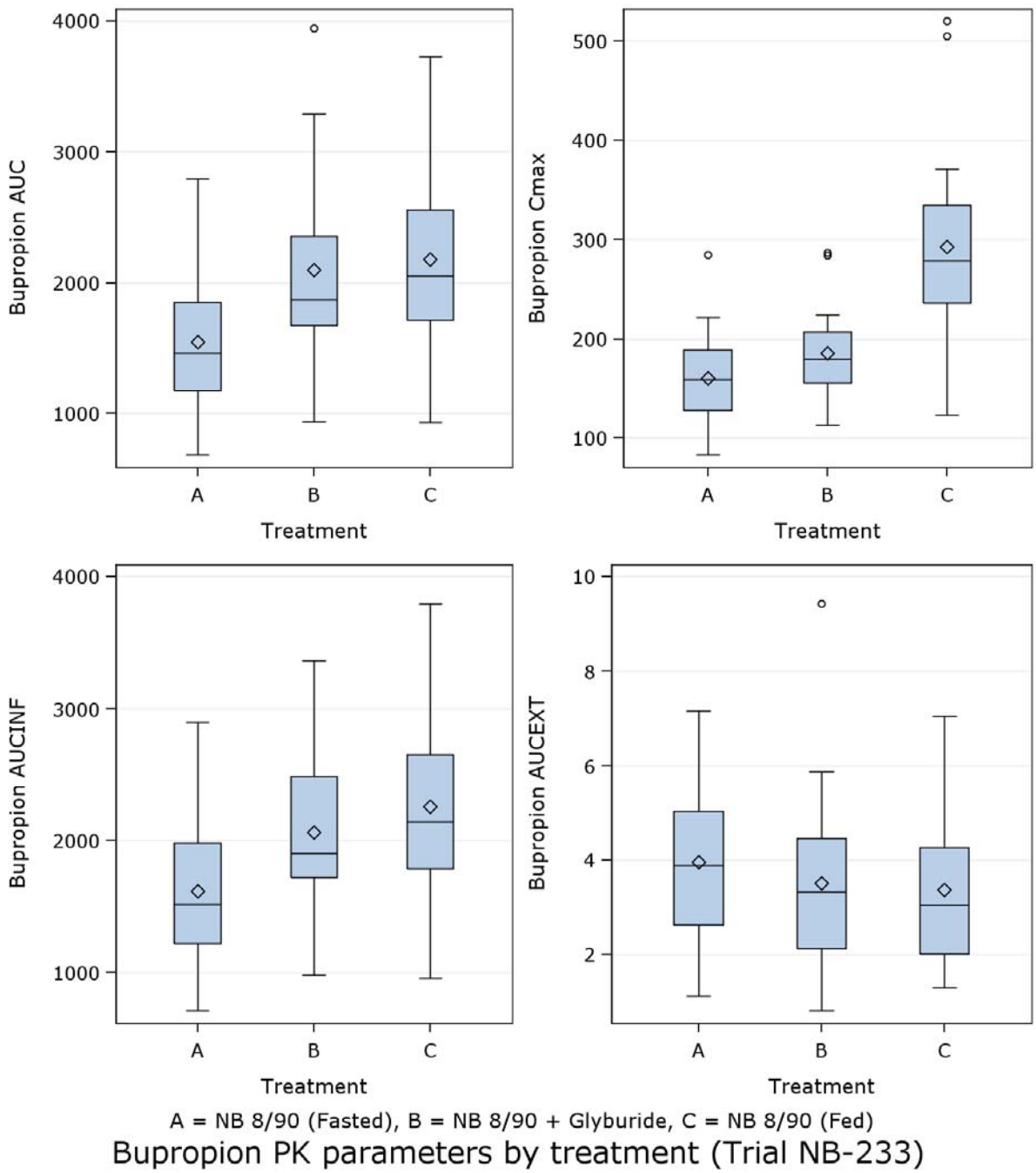
Naltrexone:



A = NB 8/90 (Fasted), B = NB 8/90 + Glyburide, C = NB 8/90 (Fed)

Naltrexone PK parameters by treatment (Trial NB-233)

Bupropion:



The AUC% extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both naltrexone and bupropion.

The geometric mean ratios and 90% CIs for the treatment comparisons are presented in the following Tables:

Table 1 Statistical comparison for naltrexone PK parameter (Fed versus Fasted)

		Geometric LS Means			
Analyte	PK Parameter	Nal SR/Bup SR, Fed	Nal SR/Bup SR, Fasted	% Geometric Mean Ratio	90% Confidence Intervals
Plasma Naltrexone	C_{max} (ng/mL)	3.63	0.98	370.57	315.66 - 435.02
	AUC_{0-t} (ng*hr/mL)	15.00	7.09	211.50	198.11 - 225.81
	$AUC_{0-\infty}$ (ng*hr/mL)	15.24	7.36	207.01	193.52 - 221.44
Plasma 6-Beta Naltrexol	C_{max} (ng/mL)	22.02	14.45	152.42	138.79 - 167.39
	AUC_{0-t} (ng*hr/mL)	245.67	216.62	113.41	109.66 - 117.29
	$AUC_{0-\infty}$ (ng*hr/mL)	259.81	233.18	111.42	108.00 - 114.95

Nal SR/Bup SR, Fed = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets, Fed (Test 2, Treatment C)
Nal SR/Bup SR, Fasted = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets, Fasted (Reference, Treatment A)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)
Subject 7 Period 1 Treatment B was excluded due to vomiting.

Table 2 Statistical comparison for bupropion PK parameter (Fed versus Fasted)

		Geometric LS Means			
Analyte	PK Parameter	Nal SR/Bup SR, Fed	Nal SR/Bup SR, Fasted	% Geometric Mean Ratio	90% Confidence Intervals
Plasma Bupropion	C_{max} (ng/mL)	274.49	152.71	179.74	159.99 - 201.93
	AUC_{0-t} (ng*hr/mL)	2037.99	1460.89	139.50	130.82 - 148.77
	$AUC_{0-\infty}$ (ng*hr/mL)	2103.04	1521.23	138.25	129.55 - 147.53
Plasma Hydroxybupropion	C_{max} (ng/mL)	290.90	275.83	105.46	98.80 - 112.58
	AUC_{0-t} (ng*hr/mL)	12474.47	11224.36	111.14	104.46 - 118.25
	$AUC_{0-\infty}$ (ng*hr/mL)	13134.37	11800.02	111.31	104.31 - 118.78
Plasma Threohydrobupropion	C_{max} (ng/mL)	131.12	104.09	125.97	114.31 - 138.81
	AUC_{0-t} (ng*hr/mL)	4595.93	4186.13	109.79	102.17 - 117.98
	$AUC_{0-\infty}$ (ng*hr/mL)	5482.90	5126.53	106.95	99.37 - 115.11
Plasma Erythrohydrobupropion	C_{max} (ng/mL)	25.00	23.98	104.23	96.72 - 112.32
	AUC_{0-t} (ng*hr/mL)	1093.57	1028.07	106.37	99.90 - 113.27
	$AUC_{0-\infty}$ (ng*hr/mL)	1194.92	1132.74	105.49	99.05 - 112.34

Nal SR/Bup SR, Fed = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets, Fed (Test 2, Treatment C)
Nal SR/Bup SR, Fasted = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets, Fasted (Reference, Treatment A)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)
Subject 7 Period 1 Treatment B was excluded due to vomiting.
$AUC_{0-\infty}$ for Subject 14 Period 3 Treatment A was excluded due to half the blood sampling interval.
$AUC_{0-\infty}$ for Subject 14 Period 2 Treatment C was excluded due to half the blood sampling interval.

Table 3 Statistical comparison for naltrexone and bupropion PK parameter (With Glyburide versus Fasted)

Statistical Comparisons of Plasma Naltrexone and Bupropion Pharmacokinetic Parameters (Pharmacokinetic Population [N = 18])

PK Parameter	% Geometric Mean Ratio (90% Confidence Interval)	
	Nal SR/Bup SR + Gly Versus Nal SR/Bup SR, Fasted	Nal SR/Bup SR, Fed Versus Nal SR/Bup SR, Fasted
Naltrexone		
C_{max}	213.89 (182.38 - 250.85)	370.57 (315.66 - 435.02)
AUC_{0-t}	198.52 (186.02 - 211.85)	211.50 (198.11 - 225.81)
$AUC_{0-\infty}$	194.61 (182.05 - 208.05)	207.01 (193.52 - 221.44)
Bupropion		
C_{max}	117.70 (104.84 - 132.13)	179.74 (159.99 - 201.93)
AUC_{0-t}	137.12 (128.63 - 146.17)	139.50 (130.82 - 148.77)
$AUC_{0-\infty}$	135.57 (126.90 - 144.84)	138.25 (129.55 - 147.53)

Nal SR/Bup SR, Fasted = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets, Fasted (Reference, Treatment A)
Nal SR/Bup SR + Gly = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Micronized Glyburide 6 mg Tablet, Fasted (Test 1, Treatment B)
Parameters were ln-transformed prior to analysis.
% Geometric Mean Ratio = 100*(test/reference).
Subject 7 Period 1 Treatment B was excluded due to vomiting.

Table 3 Descriptive Statistics of Plasma Glyburide Pharmacokinetic Parameters (Pharmacokinetic Population [N = 18])

	Nal SR/Bup SR + Gly
Pharmacokinetic Parameters	**Mean ± SD (n)**
C_{max} (ng/mL)	188 ± 29.8 (16)
T_{max} (hr)	7.02 (3.00, 10.03) (16)
$t_{1/2}$ (hr)	3.44 ± 1.53 (16)
AUC_{0-t} (ng*hr/mL)	1347.71 ± 31.35 (16)
$AUC_{0-\infty}$ (ng*hr/mL)	1368.56 ± 31.08 (16)

T_{max} presented as Median (Minimum, Maximum)
Geometric means and CV(%) are presented for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$
Nal SR/Bup SR + Gly = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Micronized Glyburide 6 mg Tablet, Fasted (Test 1, Treatment B)

Published glyburide PK parameters following a single oral dose of micronized glyburide 6 mg tablet under fasted conditions were 153.4 ng/mL (Cmax), 6.65 h (Tmax), 1102 ng*hr/mL (AUC0-∞), and 4.01 h (t1/2). (FDA, Bioequivalence Review, Application Number 74-686).

Conclusions:

- A marked food effect was observed for Nal SR/Bup SR with naltrexone AUC and Cmax increasing approximately 2- and 4-fold and bupropion AUC and Cmax increasing approximately 1.4- and 1.8-fold.
- Glyburide co-administration was associated with an increase in PK exposure of naltrexone and bupropion when given as Nal SR/Bup SR. Naltrexone AUC and Cmax increased approximately 2-fold and bupropion AUC and Cmax increased 18% and 37%, respectively. Given the food effect observed in this study, the increased exposure could be due to glyburide administration with an oral glucose solution that provided over 1000 calories (40% of the calories were in the first hour postdose).

- The PK of naltrexone and bupropion with glyburide and its accompanying glucose solution were elevated relative to the fasted condition and reduced relative to the fed condition of a high-fat, high-calorie meal.
- Both the food effect and apparent drug-drug interaction with glyburide were mitigated in part for bupropion by taking into account its active metabolites. The increases in PAWC Cmax and AUC were only 18% and 24% for glyburide co-administration. Food increased PAWC Cmax by 40% whereas AUC increased 15% with %CIs falling entirely within the 80-125% range. These changes are unlikely to be clinically significant.
- Although food increases the exposure of naltrexone, this finding is not believed to be clinically significant since subjects in the phase 3 clinical trials were instructed to take naltrexone SR/bupropion SR with food to improve tolerability. Similarly, the effect of glyburide on naltrexone (which could also be food related) is not expected to be clinically meaningful when naltrexone SR/bupropion SR is administered with food.
- Published PK results from one study of a single 6 mg dose of glyburide were not appreciably different from Nal SR/Bup SR + Gly results. Although exposure from Nal SR/Bup SR + Gly was ~24% higher, this difference is small given the comparison across studies and is not expected to be clinically significant.

Reviewer's Comments: Overall, sponsor's conclusions from this study are reasonable and acceptable with some notable exceptions. Sponsor concluded that the DDI study results were confounded by the possible food-effect on naltrexone and bupropion PK due to oral glucose solution. There is literature information that suggests that food-effect due to oral glucose solution cannot be ruled out[1]. Also, treatment comparison results and conclusions based on PAWC are not convincing considering uncertainty around PAWC metric.

[1] Linear Gastric Emptying of Hyperosmolar Glucose Solutions. William T. Phillips, Joyce G. Schwartz, Ralph Blumhardt, and C. Alex McMahan. J Nucl Med 1991; 32:377-381

1.1.7 DDI Study (NB-234)

The study NB-234 was designed with multiple assessments, which include effects of single dose of nifedipine (80 mg) or lisinopril (40 mg) on the single dose plasma PK of 2 naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets (when given alone and when co-administered with these drugs) in healthy adult subjects. In addition, the effects of naltrexone (16 mg total) and bupropion (180 mg total) on the single dose plasma PK of nifedipine or lisinopril was estimated based on comparison to any previously published or reported results of these drugs when given alone as single-dose.

Nifedipine is metabolized by CYP3A4. Hence, drugs known to either inhibit (e.g., ketoconazole, erythromycin, etc.) or induce (e.g., rifampin, carbamazepine, etc.) CYP3A4 may alter the first pass or clearance of nifedipine. The metabolites are excreted in urine and bile. Both in vitro and in vivo data indicate that nifedipine can inhibit the metabolism of other drugs that are substrates of CYP3A4; thereby increasing the exposure to other drugs. Nifedipine is available in 30 mg, 60 mg and 90 mg dosage forms. Treatment with nifedipine for either hypertension or angina should be initiated with 30 or 60 mg once daily.

Lisinopril, an oral long-acting angiotensin converting enzyme inhibitor, does not undergo metabolism and is excreted unchanged entirely in the urine. No PK-related drug interactions involving lisinopril are reported in the labeling for lisinopril tablets (Zestril®), including concomitant use with propranolol or hydrochlorothiazide. Lisinopril (Zestril®), is available as 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg tablets for oral administration. The recommended initial dose is 10 mg once a day and dose is adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose.

The highest dose was evaluated for both nifedipine and lisinopril to maximize the potential for a PK interaction with naltrexone and/or bupropion (and their metabolites) to be detected.

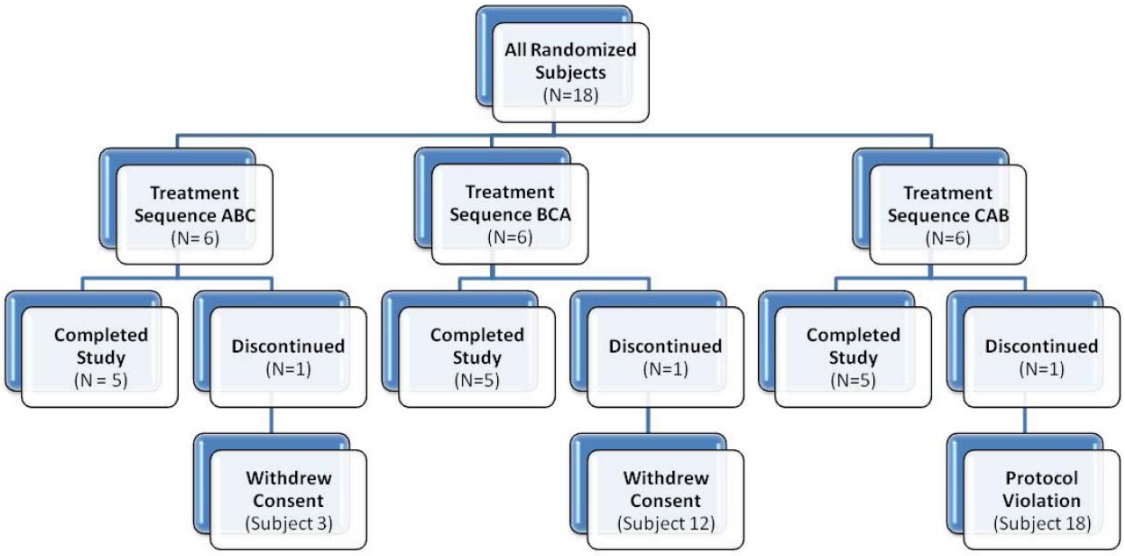
The study design is as follows:

Title:	A Phase 1, Open-Label, Randomized, Single-Dose, Three-Way Crossover Study to Assess the Effects of Nifedipine or Lisinopril on the Plasma Pharmacokinetics of Naltrexone SR/Bupropion SR Combination Trilayer Tablets in Healthy Adult Subjects
Objectives:	**Primary:** The primary objective of this study was to assess the effects of single-dose nifedipine (90 mg) extended release (ER) or lisinopril (40 mg) immediate release (IR) tablets on the single-dose plasma pharmacokinetics (PK) of 2 naltrexone 8 mg sustained release (SR)/bupropion 90 mg SR combination trilayer tablets in healthy adult subjects. **Secondary:** The secondary objectives of this study were: • To compare the single-dose plasma PK of nifedipine and lisinopril (given in combination with naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets) to previously published or reported results of these individual agents when given as monotherapy. • To assess the safety and tolerability of the 3 evaluated treatments.
Study Design	The study was conducted in a total of 18 healthy male and female subjects between the ages of 18 and 60 years, inclusive. Subjects received 3 different

	single-dose treatments. There was a minimum 14-day washout between dosing days of each treatment. Study confinement at the Phase 1 unit began the day prior to dosing, with at least a 10-hour fast prior to study drug administration. Confinement lasted for at least 72 hours after dosing for each treatment period. The 3 study treatments (A, B, and C) were as follows: A = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets (Reference) B = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets + 1 nifedipine 90 mg ER tablet (Test 1) C = Two naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets + 1 lisinopril 40 mg IR tablet (Test 2) A total of 18 subjects were randomized to 3 treatment sequences (6 subjects per sequence; Table 9-1) according to a Latin square design. The treatment sequence for each subject included all 3 treatments: Treatment A (Reference), Treatment B (Test 1), and Treatment C (Test 2).
Study Population	N= 18 Healthy subjects, Gender: 12 M and 6F, Age: 40 (24, 58) yr Weight: 82 (58-110) kg, BMI: 29 (25-39)
Test Product	Two investigational naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets, Lot #C8B0367 (manufactured by (b) (4) co-administered with 1 nifedipine 90 mg ER tablet, Lot #5401681 (Adalat® CC, Bayer) given as a single oral dose (Test 1); Two investigational naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets, Lot #C8B0367 (manufactured by (b) (4) co-administered with 1 lisinopril 40 mg IR tablet, Lot #107065 (Zestril®, Astra Zeneca) given as a single oral dose (Test 2).
Reference Products	2 investigational naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets, Lot # C8B0367 (manufactured by (b) (4), given as a single oral dose.
Sampling: Blood	Blood samples for determination of naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion plasma concentrations were measured at the following times for each treatment period: 15 minutes pre-dose (0 hour), and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 120 hours post-dose. Naltrexone elimination half-life (t1/2) is approximately 4 h, bupropion has a t1/2 of 21 hr, nifedipine has a t1/2 of 2 hr, and lisinopril has a t1/2 of ~30 hr; thus, a 120-h plasma concentration versus time profiling appears to be adequate for all analytes.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞,Cmax, Tmax, Kel, t1/2
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Protocol Deviations:
There were no protocol deviations with respect to study entry criteria, no subjects who developed withdrawal criteria and were not withdrawn, and no subjects who received the wrong treatment or incorrect dose.

Subject Disposition and Data Sets Analyzed:



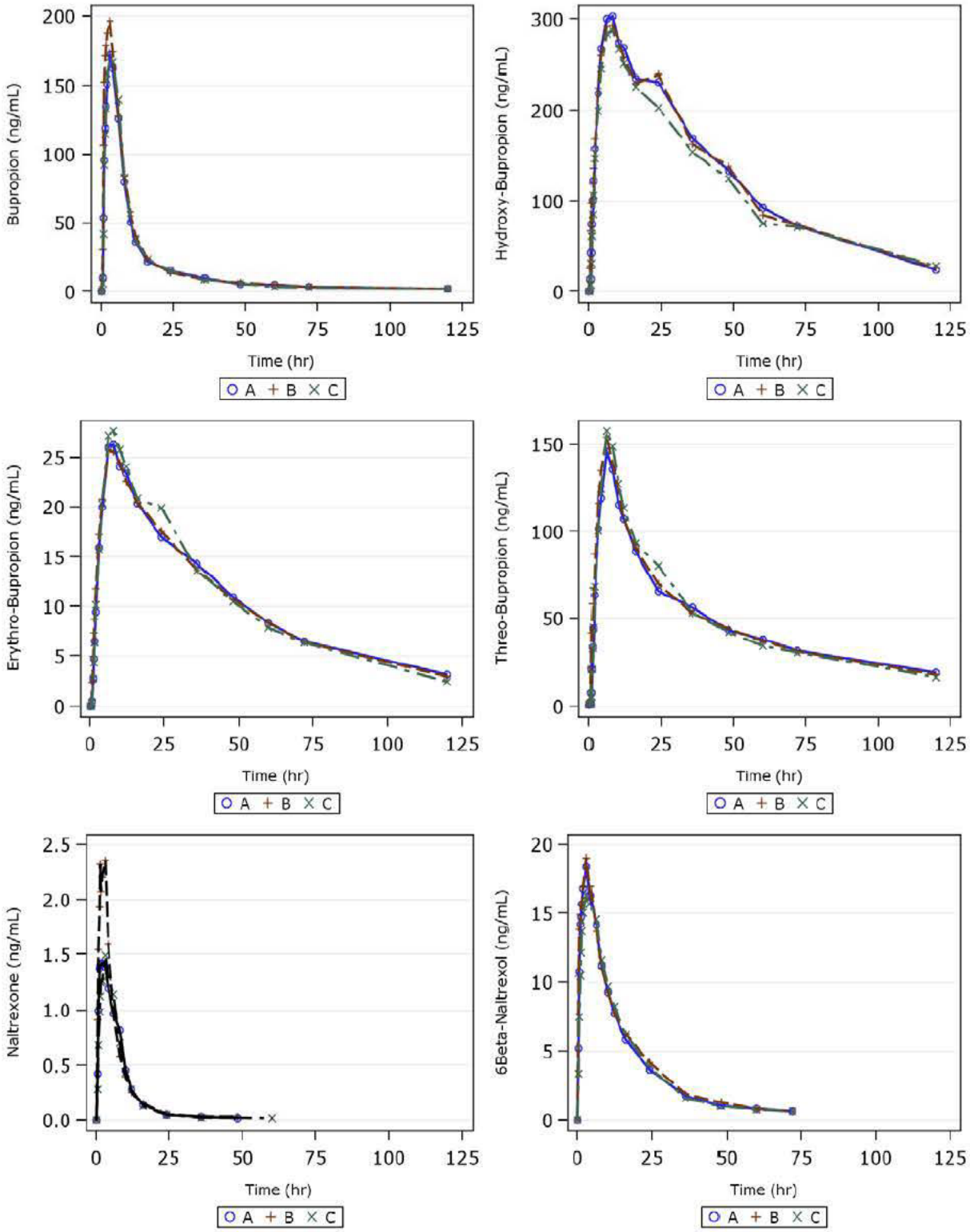
All 18 subjects who were enrolled in the study also received at least 1 formulation and were included in the PK population; however, a total of 5 subjects discontinued or were excluded from individual treatment summary statistics and statistical analysis of PK. Table below presents the subjects with missing or excluded data for individual PK treatment summary statistics and statistical analysis.

Subject Number	Treatment	Analyte(s) Affected	Reason Data is Missing or Excluded	Scope of Exclusion
2	Nal SR/Bup SR+Nif	Naltrexone, 6-beta naltrexol, bupropion and metabolites, and nifedipine	Vomiting occurred approximately 9.5 hours postdose which is within the intended dosing interval of 12 hours*	PK summary statistics and statistical analysis
3	Nal SR/Bup SR+Nif, Nal SR/Bup SR+Lis	Naltrexone, 6-beta naltrexol, bupropion and metabolites, nifedipine and lisinopril	Did not receive these treatments	PK summary statistics and statistical analysis
6	Nal SR/Bup SR+Nif	Naltrexone, 6-beta naltrexol, bupropion and metabolites, and nifedipine	Vomiting occurred approximately 4 hours postdose which is within the intended dosing interval of 12 hours*	PK summary statistics and statistical analysis
12	Nal SR/Bup SR, Nal SR/Bup SR+Nif	Naltrexone, 6-beta naltrexol, bupropion and metabolites, and nifedipine	Did not receive these treatments	PK summary statistics and statistical analysis
18	Nal SR/Bup SR	Naltrexone, 6-beta naltrexol, bupropion and metabolites	Did not receive this treatment	PK summary statistics and statistical analysis

Nal SR/Bup SR: Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Reference, Treatment A)
Nal SR/Bup SR+Nif: Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Nifedipine 90 mg ER Tablet (Test 1, Treatment B)
Nal SR/Bup SR+Lis: Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Lisinopril 40 mg IR Tablet (Test 2, Treatment C)
* According to the Food and Drug Administration's (FDA) *Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (2003)*, in the case of modified-release products, the data from subjects who experienced emesis any time during the labeled dosing interval should be deleted from the analysis.

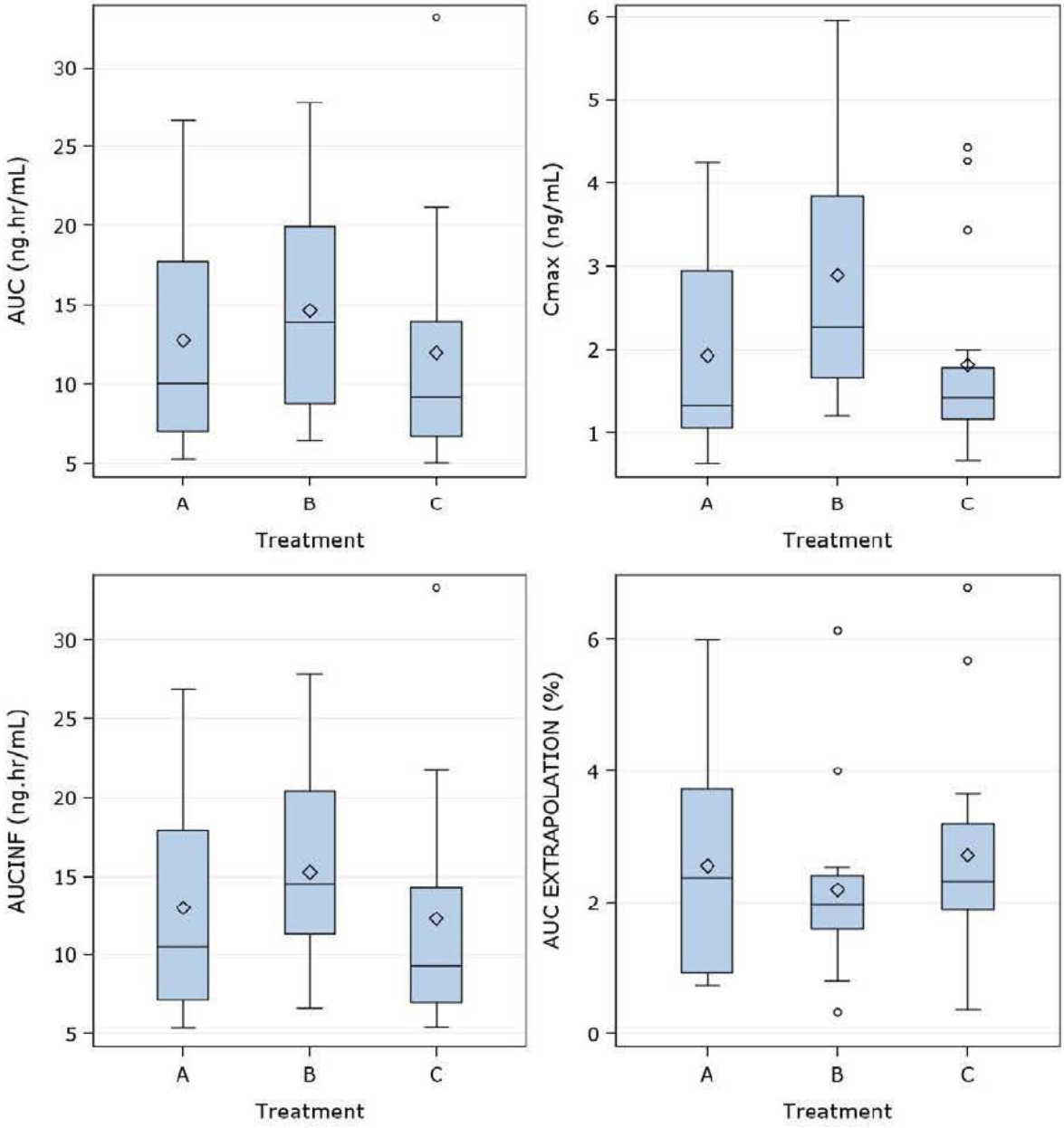
Pharmacokinetic Results:

The concentration-time profiles of all analytes by treatment are shown in Figure below:



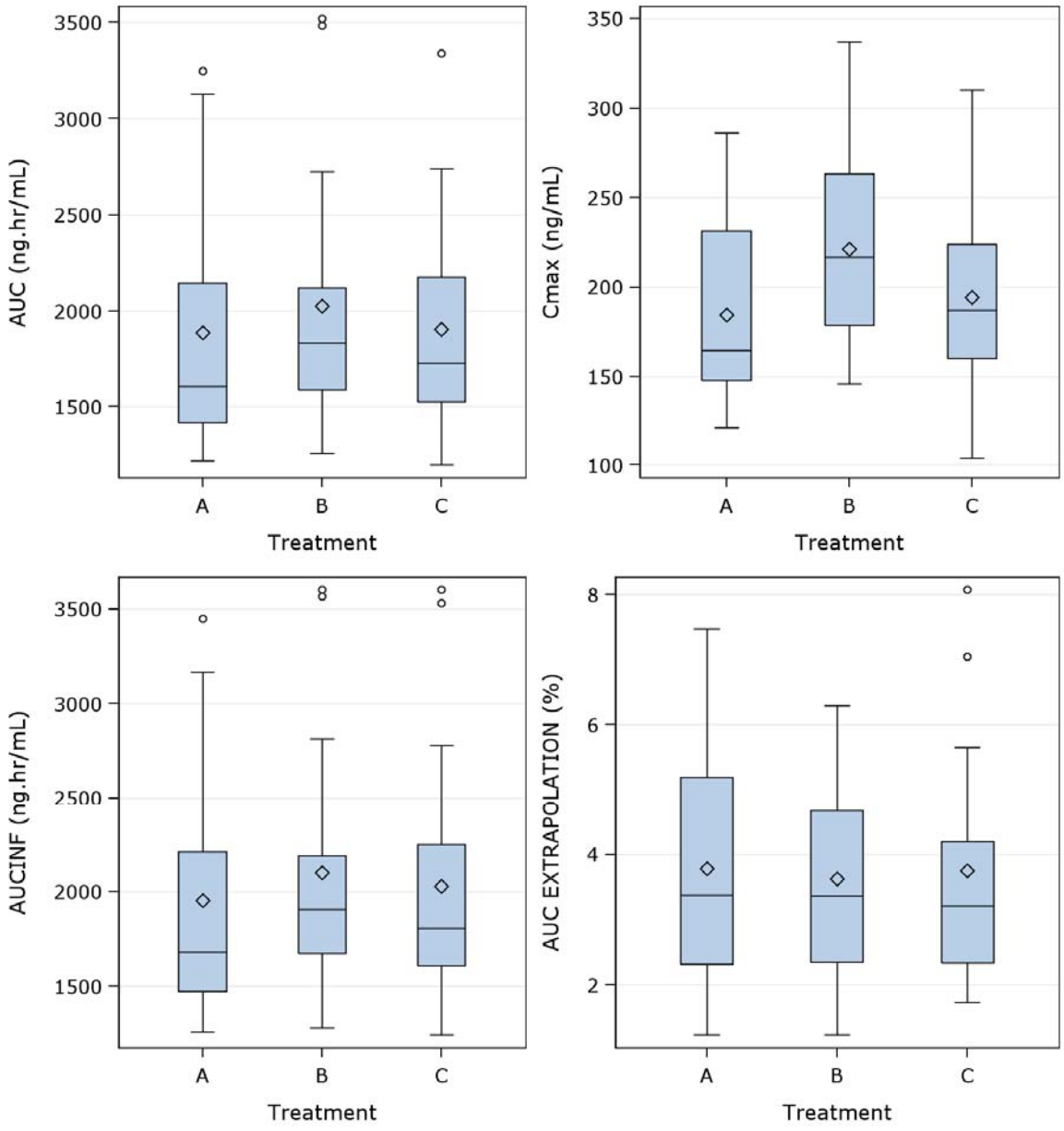
A = 2 x NB 8/90, B = 2 x NB 8/90 with Nifedipine, C = 2 x NB 8/90 with Lisinopril
Mean Concentration-time Plots by Treatment (Trial NB-234)

The distribution of PK parameters by treatment for naltrexone and bupropion is summarized in the figures below:



A = 2 x NB 8/90, B = 2 x NB 8/90 with Nifedipine, C = 2 x NB 8/90 with Lisinopril

Naltrexone PK parameters by treatment (Trial NB-234)



The AUC % extrapolated was comparable across the two treatments to enable unbiased comparison of AUC0-inf for both naltrexone and bupropion.

The statistical comparison of PK parameters of naltrexone and bupropion are given in the following tables:

Table 1 Statistical comparison for naltrexone PK parameter (NB + Nifedipine versus NB Alone)

Plasma Analyte	PK Parameters	Nal SR/Bup SR	Nal SR/Bup SR + Nif	%MR (90% CI)‡
Naltrexone	C_{max} (ng/mL)	1.91 ± 1.09 (16)	2.74 ± 1.44 (14)	158.30 (135.05 – 185.55)
	T_{max} (hr)	1.43 (0.75, 8.00) (16)	1.34 (0.50, 3.01) (14)	N/A
	$t_{1/2}$ (hr)	5.26 ± 2.01 (15)	4.97 ± 1.55 (14)	N/A
	AUC_{0-t} (ng*hr/mL)	12.52 ± 6.81 (16)	14.80 ± 6.92 (14)	126.59 (110.42 – 145.13)
	$AUC_{0-\infty}$ (ng*hr/mL)	13.03 ± 6.94 (15)	15.09 ± 6.92 (14)	123.68 (107.55 – 142.23)
6-Beta Naltrexol	C_{max} (ng/mL)	19.3 ± 7.00 (16)	20.1 ± 5.32 (14)	112.96 (103.58 – 123.19)
	T_{max} (hr)	2.00 (1.00, 6.00) (16)	3.00 (0.50, 4.00) (14)	N/A
	$t_{1/2}$ (hr)	13.14 ± 2.72 (16)	13.27 ± 3.64 (14)	N/A
	AUC_{0-t} (ng*hr/mL)	274.50 ± 68.29 (16)	289.36 ± 67.03 (14)	109.68 (103.15 – 116.62)
	AUC0-∞ (ng*hr/mL)	288.29 ± 67.89 (16)	303.75 ± 69.55 (14)	109.28 (103.00 - 115.95)

N/A = Not Applicable
PK data are means ± SD (N) whereas T_{max} is presented as Median (Minimum, Maximum) (N).
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Treatment A, Reference) Nal SR/Bup SR + Nif= Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Nifedipine 90 mg ER Tablet (Treatment B, Test 1)
Subject 2 Period 1 Treatment B was excluded from 90% CI and % MR calculation due to vomiting.
Subject 6 Period 1 Treatment B was excluded from 90% CI and % MR calculation due to vomiting.

Table 2 Statistical comparison for naltrexone PK parameter (NB + Lisinopril versus NB Alone)

Plasma Analyte	PK Parameters	Nal SR/Bup SR	Nal SR/Bup SR + Lis	%MR (90% CI)‡
Naltrexone	C_{max} (ng/mL)	1.91 ± 1.09 (16)	1.81 ± 1.13(17)	103.80 (89.34 – 120.62)
	T_{max} (hr)	1.43 (0.75, 8.00) (16)	3.00 (1.25, 6.00) (17)	N/A
	$t_{1/2}$ (hr)	5.26 ± 2.01 (15)	4.34 ± 1.93 (17)	N/A
	AUC_{0-t} (ng*hr/mL)	12.52 ± 6.81 (16)	11.98 ± 7.27 (17)	99.87 (87.77 – 113.64)
	$AUC_{0-\infty}$ (ng*hr/mL)	13.03 ± 6.94 (15)	12.26 ± 7.29 (17)	98.37 (86.21 – 112.25)
6-Beta Naltrexol	C_{max} (ng/mL)	19.3 ± 7.00 (16)	19.5 ± 5.57 (17)	105.75 (97.44 – 114.78)
	T_{max} (hr)	2.00 (1.00, 6.00) (16)	2.00 (1.25, 6.00) (17)	N/A
	$t_{1/2}$ (hr)	13.14 ± 2.72 (16)	12.38 ± 3.32 (17)	N/A
	AUC_{0-t} (ng*hr/mL)	274.50 ± 68.29 (16)	268.34 ± 59.70 (17)	102.79 (97.00 – 108.93)
	$AUC_{0-\infty}$ (ng*hr/mL)	288.29 ± 67.89 (16)	281.54 ± 60.99 (17)	102.42 (96.84 – 108.32)

N/A = Not Applicable
PK data are means ± SD (N) whereas T_{max} is presented as Median (Minimum, Maximum).
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Treatment A, Reference)
Nal SR/Bup SR + Lis = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Lisinopril 40 mg IR Tablet (Treatment C, Test 2)

Table 3 Statistical comparison for bupropion PK parameter (NB + Nifedipine versus NB Alone)

Plasma Analyte	PK Parameters	Nal SR/Bup SR	Nal SR/Bup SR + Nif	%MR (90% CI)‡
Bupropion	C_{max} (ng/mL)	185 ± 53.9 (16)	214 ± 53.8 (14)	121.57 (111.44 – 132.62)
	T_{max} (hr)	3.00 (1.50, 6.00) (16)	2.00 (0.76, 4.00) (14)	N/A
	$t_{1/2}$ (hr)	23.71 ± 7.31 (15)	22.71 ± 7.70 (14)	N/A
	AUC_{0-t} (ng*hr/mL)	1890.23 ± 663.27 (16)	1994.58 ± 695.01 (14)	109.52 (102.95 – 116.51)
	$AUC_{0-\infty}$ (ng*hr/mL)	1994.17 ± 688.23 (15)	2065.58 ± 704.67 (14)	110.83 (104.18 – 117.90)
Hydroxybupropion	C_{max} (ng/mL)	311 ± 129 (16)	295 ± 129 (14)	96.03 (88.66 - 104.01)
	T_{max} (hr)	8.00 (4.00, 12.00) (16)	7.00 (6.00, 12.00) (14)	N/A
	$t_{1/2}$ (hr)	31.29 ± 10.45 (16)	27.72 ± 7.47 (13)	N/A
	AUC_{0-t} (ng*hr/mL)	14465.70 ± 5935.07 (16)	14165.33 ± 7595.14 (14)	95.75 (85.98 – 106.63)
	$AUC_{0-\infty}$ (ng*hr/mL)	15921.37 ± 6793.32 (16)	15339.44 ± 8671.99 (13)	94.53 (84.58 – 105.64)
Threohydrobupropion	C_{max} (ng/mL)	148 ± 55.9 (16)	153 ± 43.5 (14)	111.10 (101.97 – 121.06)
	T_{max} (hr)	6.00 (4.00, 8.00) (16)	6.00 (3.00, 8.04) (14)	N/A
	$t_{1/2}$ (hr)	52.88 ± 17.39 (15)	54.61 ± 15.92 (14)	N/A
	AUC_{0-t} (ng*hr/mL)	5754.77 ± 1810.51 (16)	5538.79 ± 1599.68 (14)	99.22 (90.45 - 108.83)
	$AUC_{0-\infty}$ (ng*hr/mL)	7332.95 ± 2378.51 (15)	7153.70 ± 2411.89 (14)	101.42 (93.06 – 110.53)
Erythrohydrobupropion	C_{max} (ng/mL)	27.4 ± 7.44 (16)	26.5 ± 5.08 (14)	100.22 (92.54 – 108.54)
	T_{max} (hr)	8.00 (6.00, 12.00) (16)	8.00 (6.00, 10.00) (14)	N/A
	$t_{1/2}$ (hr)	34.97 ± 10.83 (16)	33.41 ± 12.06 (13)	N/A
	AUC_{0-t} (ng*hr/mL)	1215.21 ± 421.67 (16)	1195.75 ± 392.19 (14)	102.31 (92.58 - 113.07)
	$AUC_{0-\infty}$ (ng*hr/mL)	1391.94 ± 507.73 (16)	1380.42± 551.13 (13)	101.83 (93.55 – 110.84)

N/A = Not Applicable
PK data are means ± SD (N) whereas T_{max} is presented as Median (Minimum, Maximum) (N).
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Treatment A, Reference)
Nal SR/Bup SR + Nif= Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Nifedipine 90 mg ER Tablet (Treatment B, Test 1)

Table 4 Statistical comparison for bupropion PK parameter (NB + Lisinopril versus NB Alone)

Plasma Analyte	PK Parameters	Nal SR/Bup SR	Nal SR/Bup SR + Lis	%MR (90% CI)‡
Bupropion	C_{max} (ng/mL)	185 ± 53.9 (16)	194 ± 59.6 (17)	104.05 (95.84 – 112.96)
	T_{max} (hr)	3.00 (1.50, 6.00) (16)	3.00 (1.99, 6.00) (17)	N/A
	$t_{1/2}$ (hr)	23.71 ± 7.31 (15)	22.85 ± 8.02 (16)	N/A
	AUC_{0-t} (ng*hr/mL)	1890.23 ± 663.27 (16)	1907.37 ± 585.45 (17)	102.18 (96.38 – 108.34)
	$AUC_{0-\infty}$ (ng*hr/mL)	1994.17 ± 688.23 (15)	1929.86 ± 587.56 (16)	104.16 (98.15 – 110.54)
Hydroxybupropion	C_{max} (ng/mL)	311 ± 129 (16)	294 ± 119 (17)	97.56 (90.47 – 105.21)
	T_{max} (hr)	8.00 (4.00, 12.00) (16)	8.00 (4.00, 10.00) (17)	N/A
	$t_{1/2}$ (hr)	31.29 ± 10.45 (16)	30.47 ± 8.11 (16)	N/A
	AUC_{0-t} (ng*hr/mL)	14465.70 ± 5935.07 (16)	13537.14 ± 5993.26 (17)	94.77 (85.60 – 104.92)
	$AUC_{0-\infty}$ (ng*hr/mL)	15921.37 ± 6793.32 (16)	14370.90 ± 6610.09 (16)	96.39 (86.78 – 107.06)
Threohydrobupropion	C_{max} (ng/mL)	148 ± 55.9 (16)	163 ± 50.7 (17)	110.40 (101.79 – 119.73)
	T_{max} (hr)	6.00 (4.00, 8.00) (16)	6.00 (4.00, 8.01) (17)	N/A
	$t_{1/2}$ (hr)	52.88 ± 17.39 (15)	52.80 ± 16.78 (16)	N/A
	AUC_{0-t} (ng*hr/mL)	5754.77 ± 1810.51 (16)	5573.88 ± 1314.87 (17)	97.56 (89.40 – 106.47)
	$AUC_{0-\infty}$ (ng*hr/mL)	7332.95 ± 2378.51 (15)	7030.70 ± 1911.67 (16)	97.09 (89.28 - 105.59)
Erythrohydrobupropion	C_{max} (ng/mL)	27.4 ± 7.44 (16)	28.9 ± 5.90 (17)	105.65 (97.98 – 113.92)
	T_{max} (hr)	8.00 (6.00, 12.00) (16)	6.02 (4.01, 10.00) (17)	N/A
	$t_{1/2}$ (hr)	34.97 ± 10.83 (16)	33.31 ± 8.62 (17)	N/A
	AUC_{0-t} (ng*hr/mL)	1215.21 ± 421.67 (16)	1180.96 ± 338.44 (17)	98.78 (89.87- 108.56)
	$AUC_{0-\infty}$ (ng*hr/mL)	1391.94 ± 507.73 (16)	1352.12 ± 448.57 (17)	98.19 (90.82 – 106.16)

N/A = Not Applicable
PK data are means ± SD (N) whereas T_{max} is presented as Median (Minimum, Maximum).
‡ 90% CI and % Mean Ratios (% MR) were calculated based on ln-transformed parameters.
Nal SR/Bup SR = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Treatment A, Reference)
Nal SR/Bup SR + Lis = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets + One Lisinopril 40 mg IR Tablet (Treatment C, Test 2)

Table 5 Pharmacokinetic Parameters of Nifedipine - Comparison with Literature Data

	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
NB-234[a]	1623.33 (728.09)	114 (56.4)	4.00 (3.00 – 10.00)	8.17 (2.33)
FDA[b]	1447 (737)	105 (67)	5.0 (2.7)	7.7 (3.2)
Drug label	NA	115	NA	NA

bData from Food and Drug Administration (FDA) Clinical Pharmacology and Biopharmaceutics Review. Application number 76-070 (Nifedipine extended-release tablets).

Table 6 Pharmacokinetic Parameters of Lisinopril - Comparison with Literature Data

	Dose (mg)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
NB-234[a]	40	2372.97 (966.37)	2527.29 (1049.94)	148.60 (52.73)	6.00 (4.00 – 8.17)	35.59 (14.62)
FDA[b]	20	1453	NA	110.5	6.0	NA
	30	1601	NA	124.7	6.0	NA
Noble et al	20	1231[c] (50%)	NA	86 (55%)	6-8	30
(b) (4) data on file	40	2350 (35%)	2420 (35%)	180 (40%)	6.5 (15%)	24 (40%)

bData from FDA Clinical Pharmacology and Biopharmaceutics Review Application Numbers NDA 19-777/S-037 and 19-777/S-044 (lisinopril tablets)

Conclusions:

- Co-administration of 2 naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets with a single dose of 1 nifedipine 90 mg ER tablet had no effect on bupropion systemic exposure (AUC) and resulted in increases that were not expected to be clinically meaningful in the peak plasma concentrations of naltrexone and bupropion and in the systemic exposure (AUCs) of naltrexone.
- Co-administration of 1 lisinopril 40 mg IR tablet with 2 naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets had no effect on the PK of naltrexone or bupropion when compared to 2 naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets administered alone in healthy adult subjects.
- Comparison with the literature data showed that co-administration of a single dose of 2 naltrexone SR 8 mg/bupropion SR 90 mg trilayer tablets in combination with 1 nifedipine 90 mg ER tablet appeared to have no effect on the PK of nifedipine. Similarly, co-administration of a single dose of 2 naltrexone SR 8 mg/bupropion SR 90 mg tablets in combination with 1 lisinopril 40 mg IR tablet showed lisinopril PK appeared to be comparable to the literature data.
- Two naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets co-administered with 1 nifedipine 90 mg ER tablet appeared generally safe and fairly well tolerated by the healthy male and female subjects in this study. Gastrointestinal AEs were more frequent in this group.
- Two naltrexone SR 8 mg/bupropion SR 90 mg combination trilayer tablets co-administered with 1 lisinopril 40 mg IR tablet appeared generally safe and well tolerated by the healthy male and female subjects in this study.

Sponsor's conclusions from this study are reasonable and acceptable.

1.1.8 DDI Study and multiple-dose PK (NB-236)

Bupropion and its metabolites are known to inhibit CYP2D6. To address the DDI potential of Contrave with CYP2D6 substrate, this study was conducted with Metoprolol, which is often used as the CYP2D6 substrate representing this class. The trial was conducted in subjects genotyped as extensive CYP2D6 metabolizers under the steady-state for bupropion to assess the true effect of inhibition by total daily dose of Contrave (2 x NB 8/90 mg). Bupropion was given with moderate fat diet and as a second objective sponsor also evaluated food effect at steady-state.

The study design is as follows:

Title:	A Phase 1, Open-Label, Steady-State Study to Assess the Effects of Naltrexone SR/Bupropion SR Combination Trilayer Tablets on the Single-Dose Plasma Pharmacokinetics of Metoprolol in Healthy Adult Subjects Genotyped as Extensive Metabolizers of CYP2D6
Objectives:	**Primary:** The primary objective of this study was to assess the effect of steady-state dosing of 2 naltrexone 8 mg sustained release (SR)/bupropion 90 mg SR combination trilayer tablets given twice daily on the single-dose plasma pharmacokinetics (PK) of metoprolol (50 mg) under fed conditions in healthy adult subjects genotyped as CYP2D6 extensive metabolizers. Secondary: The secondary objectives of this study were: • To assess the plasma PK of naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets under fed and fasted conditions; • To compare the steady-state plasma PK of 2 naltrexone 8 mg SR/bupropion 90 mg SR combination trilayer tablets given twice daily in the absence and presence of a single dose of metoprolol (50 mg) under fed conditions; • To assess the safety and tolerability of the treatments received throughout the duration of the study.
Study Design	The 3 study treatments (A, B, and C) were as follows: A = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Test) B = One Naltrexone IR 50 mg Tablet (Reference 1) C = One Bupropion SR 150 mg Tablet (Reference 2) During the study, subjects were dosed in the fed state on Day 1 and Days 3 - 31. On Days 3, 30, and 31, the meal consisted of a moderate-fat (23% fat), moderate-calorie (575 calories) meal.
Study Population	N= 18 Healthy subjects, Gender: 11 M and 7 F, Age: 31 (19-45) yr Weight: 87 (62-116) kg, BMI: 29 (21-38) PK Extension: N= 11 Healthy subjects, Gender: 7 M and 4 F, Age: 34 (19-45) yr Weight: 89 (62-116) kg, BMI: 29 (21-38)
Test Product	• Metoprolol (Lopressor®) 50 mg IR tablets, Lot number F0134, manufactured by Novartis Pharmaceuticals Corporation. • Naltrexone 8 mg SR/bupropion 90 mg SR trilayer combination tablets, Lot number C8B0367, manufactured by (b) (4)
Reference Products	NA

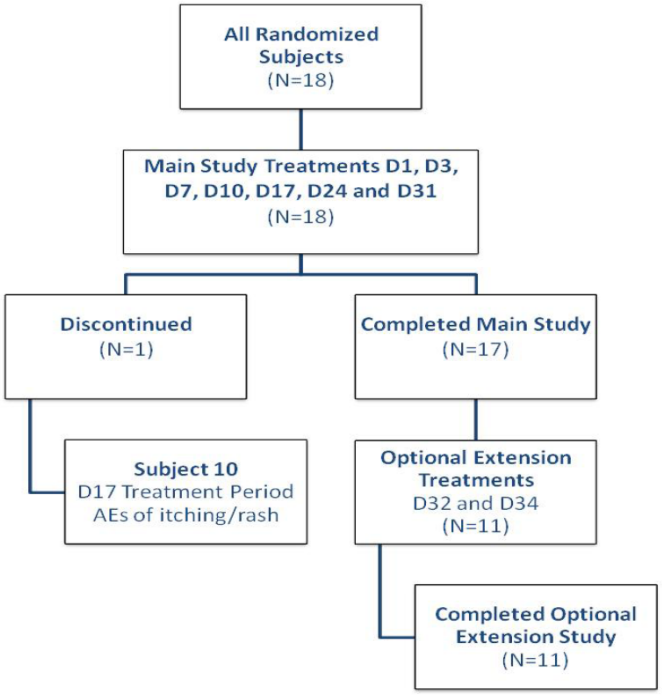
Sampling: Blood	Serial PK blood samples were collected at designated times following the morning dose on Days 1 and 31 for metoprolol (24 hours of sampling), and on Days 3 (24 hours of sampling), 30 (12 hours of sampling) and 31 (12 hours of sampling), for naltrexone, bupropion and their metabolites. In addition, trough concentrations were collected at predose (morning and evening) of Days 28 to 30 for steady-state assessment of naltrexone, bupropion and their metabolites.
Urine	none
Feces	none
PK Assessments	AUC0-t, AUC%extrapolated, AUC0-∞,AUC0-12, Cmax, Tmax, Kel, t1/2, Cavg, AUMC, CL/F, Vss/F, M/P Ratios
Safety Assessment	Vital signs, ECG , Clinical laboratory, AEs
PD Assessment	none

Summary of study plan:

Day 1	Single (morning) dose of a metoprolol 50 mg IR tablet followed by a 2-day washout period (fed).
Days 3 to 9	Once daily (morning) doses of 1 naltrexone 8 mg SR /bupropion 90 mg SR combination trilayer tablet (fed).
Days 10 to 16	Twice daily (morning and evening) doses of 1 naltrexone 8 mg SR bupropion 90 mg SR combination trilayer tablet (fed).
Days 17 to 23	Morning doses of 2 naltrexone 8 mg SR /bupropion 90 mg SR combination trilayer tablets and evening doses of 1 naltrexone 8 mg SR /bupropion 90 mg SR combination trilayer tablet (fed).
Days 24 to 30	Twice daily (morning and evening) doses of 2 naltrexone 8 mg SR /bupropion 90 mg SR combination trilayer tablets (fed).
Day 31	Twice daily (morning and evening) doses of 2 naltrexone 8 mg SR/ bupropion 90 mg SR combination trilayer tablets. Single (morning) dose of a metoprolol 50 mg IR tablet (fed).
Day 32	Twice daily (morning and evening) doses of 2 naltrexone SR 8 mg/bupropion 90 mg SR combination trilayer tablets (fed).
Day 33	Twice daily (morning and evening) doses of 2 naltrexone SR 8 mg/bupropion 90 mg SR combination trilayer tablets. The evening dose was given in the fed state and the morning dose was given in the fed or fasted state dependent on the randomization.
Day 34	Morning dose of 2 naltrexone SR 8 mg/bupropion 90 mg SR combination trilayer tablets given in the fed or fasted state dependent on the randomization.

Protocol Deviations: There were no protocol deviations with respect to study entry criteria, subjects who developed withdrawal criteria and were not withdrawn, or subjects who received the wrong treatment or incorrect dose. The Day 31 24-hour blood samples for metoprolol analysis were inadvertently not collected from the 11 subjects who continued into the optional study extension, which resulted in potential underestimation of the Day 31 to Day 1 AUC0-t ratios in those subjects, and thus the overall mean AUC0-t ratio for the metoprolol comparison. However, given that Cmax and AUC0-8 were unaffected these missing 24-hour samples have no impact on study conclusions.

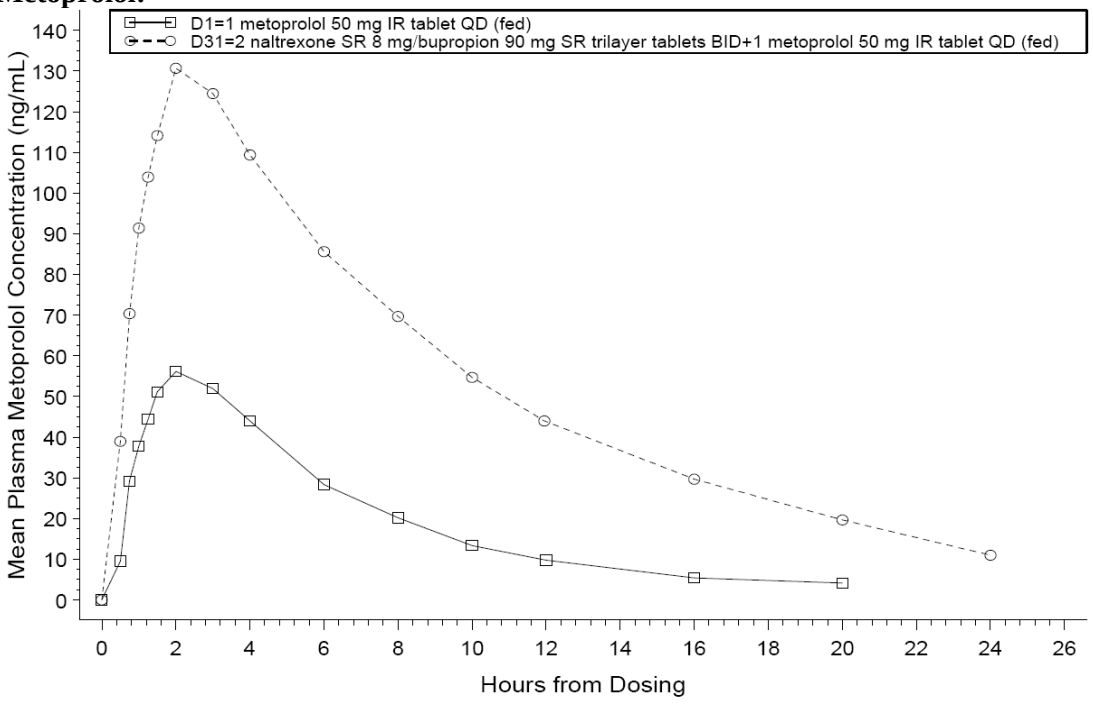
Subject Disposition and Data Sets Analyzed:



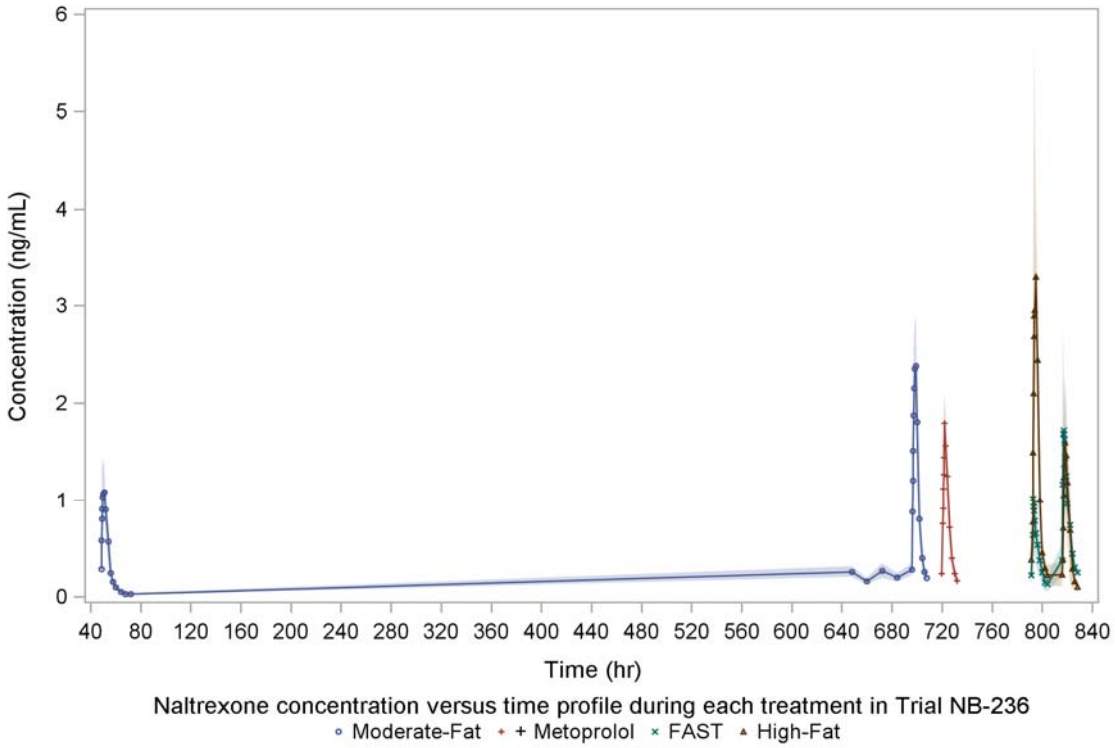
Pharmacokinetic Results:

The concentration-time profiles of all analytes by treatment are shown in Figure below:

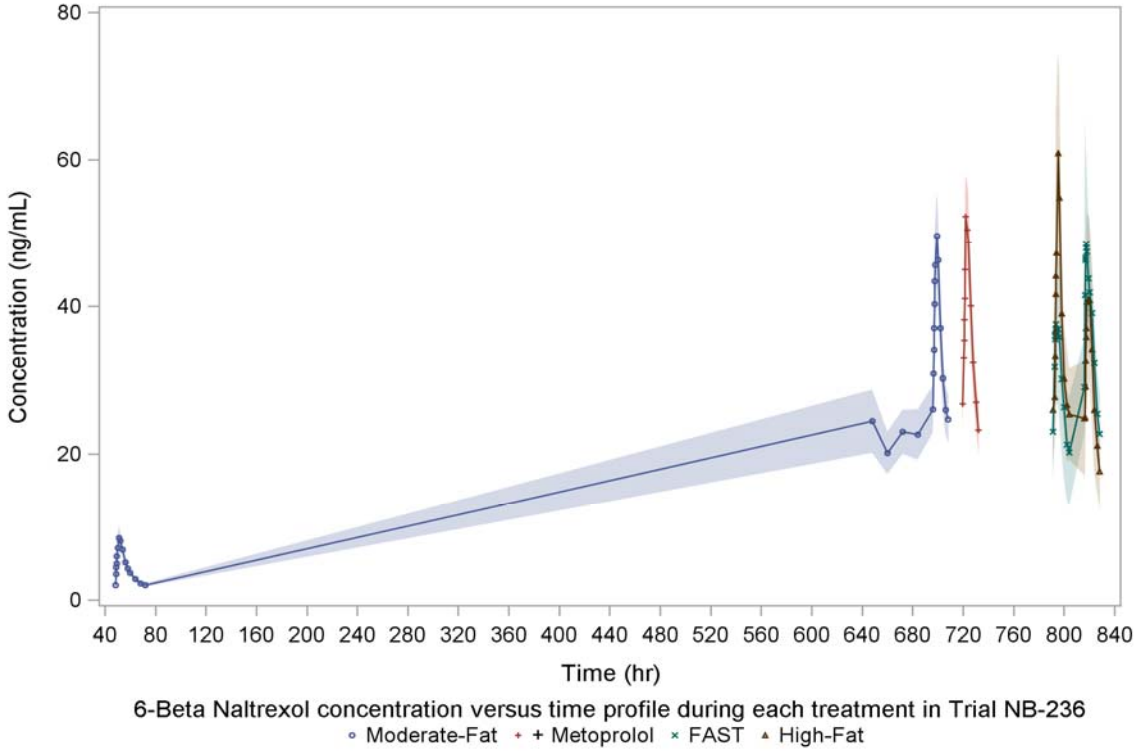
Metoprolol:



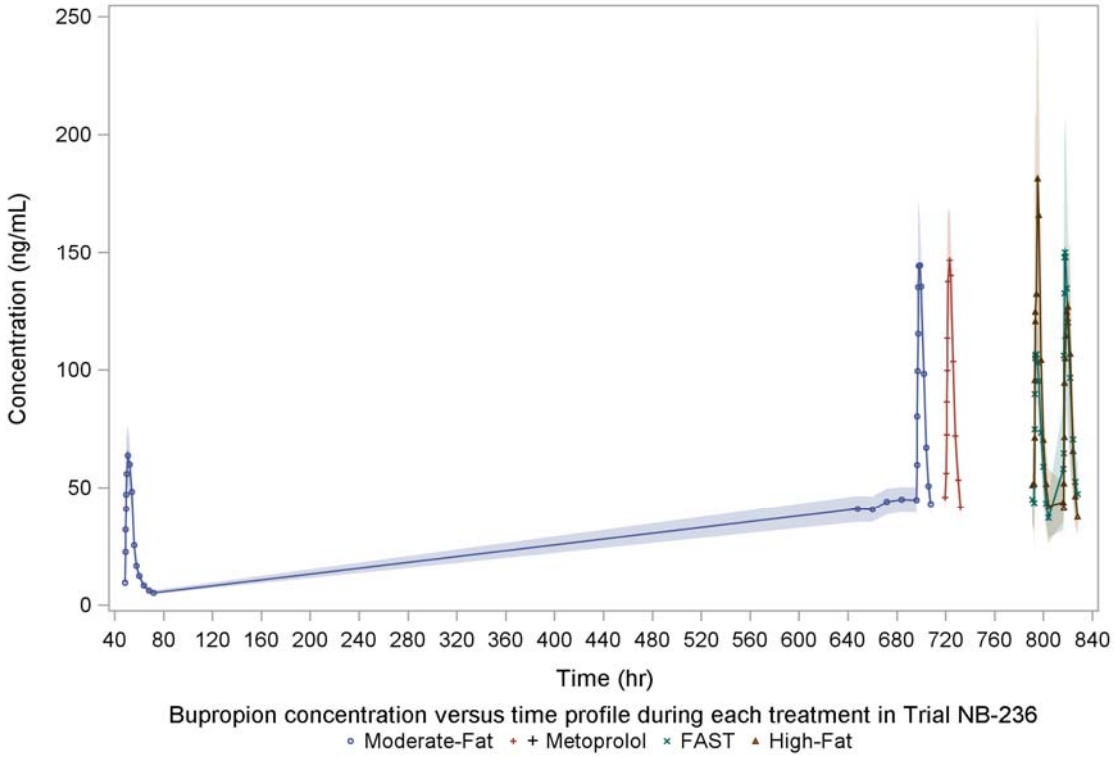
Naltrexone: (First Dose of Contrave (1 x NB 8/90 mg) on Day 3 to Last dose (2 x NB 8/90 mg) in the Extension Phase)



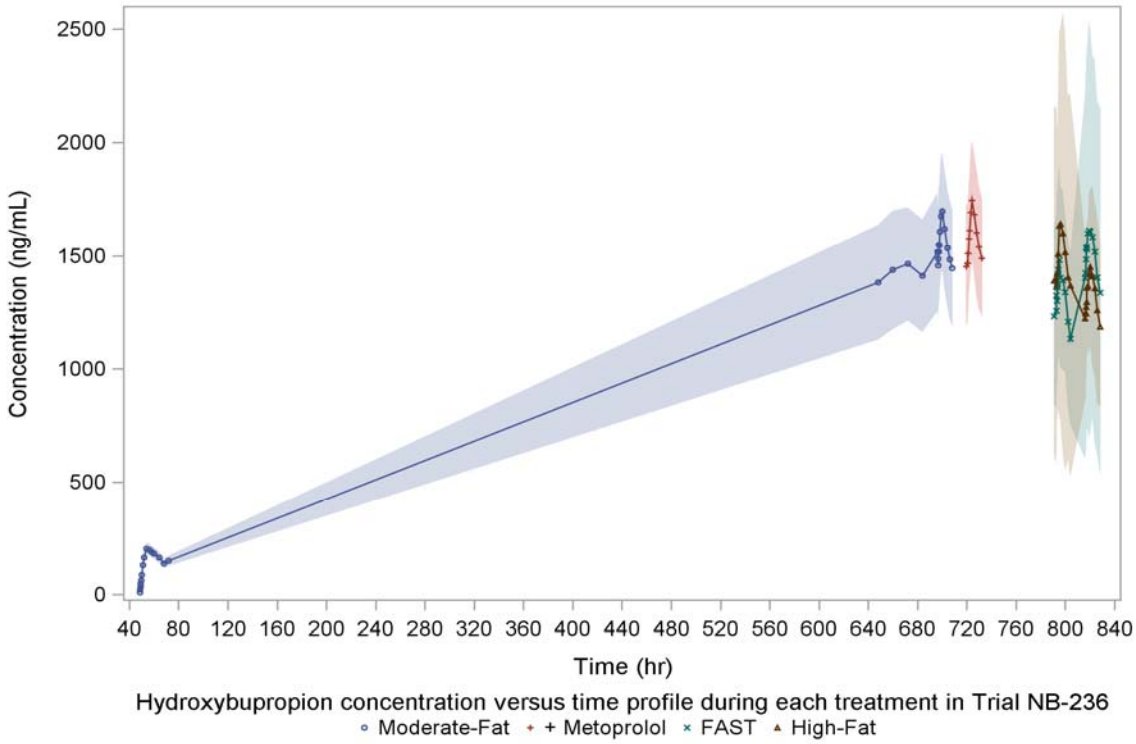
6beta-Naltrexol: ((First Dose of Contrave (1 x NB 8/90 mg) on Day 3 to Last dose (2 x NB 8/90 mg) in the Extension Phase)



Bupropion: (First Dose of Contrave (1 x NB 8/90 mg) on Day 3 to Last dose (2 x NB 8/90 mg) in the Extension Phase)



Hydroxybupropion: ((First Dose of Contrave (1 x NB 8/90 mg) on Day 3 to Last dose (2 x NB 8/90 mg) in the Extension Phase)



The results of statistical comparison are presented in tables below:

Drug-drug Interaction Comparisons:

Table 1 Statistical comparison for naltrexone PK parameters for NB+ Metoprolol (Day 31) versus NB Alone (Day 30)

Pharmacokinetic Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals
	Day 31	D24 (PK Day 30)		
Plasma Naltrexone				
C_{max} (ng/mL)	1.79	2.52	71.11	65.33 - 77.40
C_{min} (ng/mL)	0.14	0.17	80.73	70.81 - 92.03
AUC_{0-12} (ng*hr/mL)	8.68	11.52	75.40	71.36 - 79.66
Plasma 6-Beta Naltrexol				
C_{max} (ng/mL)	52.99	50.45	105.03	102.43 - 107.71
C_{min} (ng/mL)	21.89	22.94	95.39	90.13 - 100.95
AUC_{0-12} (ng*hr/mL)	434.70	413.17	105.21	102.37 - 108.13

PK Day 30 = Treatment D24 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID (fed) (Reference)
Day 31 = Treatment D31 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID + 1 metoprolol 50 mg IR QD (fed) (Test)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

Table 2 Statistical comparison for bupropion PK parameters for NB+ Metoprolol (Day 31) versus NB Alone (Day 30)

Pharmacokinetic Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals
	Day 31	D24 (PK Day 30)		
Plasma Bupropion				
C_{max} (ng/mL)	150.19	152.54	98.46	94.57 - 102.52
C_{min} (ng/mL)	39.95	40.45	98.77	95.73 - 101.91
AUC_{0-12} (ng*hr/mL)	1067.34	1059.20	100.77	99.01 - 102.56
Plasma Hydroxybupropion				
C_{max} (ng/mL)	1711.87	1672.11	102.38	100.01 - 104.80
C_{min} (ng/mL)	1338.55	1340.55	99.85	97.78 - 101.97
AUC_{0-12} (ng*hr/mL)	18400.05	17962.32	102.44	100.36 - 104.56
Plasma Threohydrobupropion				
C_{max} (ng/mL)	766.36	729.69	105.03	102.07 - 108.07
C_{min} (ng/mL)	565.89	553.39	102.26	99.66 - 104.92
AUC_{0-12} (ng*hr/mL)	8149.42	7704.88	105.77	103.30 - 108.30
Plasma Erythrohydrobupropion				
C_{max} (ng/mL)	155.98	146.72	106.31	103.36 - 109.36
C_{min} (ng/mL)	120.90	118.10	102.37	99.55 - 105.27
AUC_{0-12} (ng*hr/mL)	1698.39	1581.39	107.40	104.77 - 110.09

PK Day 30 = Treatment D24 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID (fed) (Reference)
Day 31 = Treatment D31 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID + 1 metoprolol 50 mg IR QD (fed) (Test)
Parameters were ln-transformed prior to analysis.
Geometric least- squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

Table 3 Statistical comparison for naltrexone PK parameters for NB + Metoprolol (Day 31) versus Metoprolol Alone (Day 1)

Summary and Statistical Analysis of Plasma Metoprolol Pharmacokinetic Parameters: Naltrexone/Bupropion + Metoprolol (Day 31) Versus Metoprolol Alone (Day 1) (Pharmacokinetic Population [N = 18])

Plasma Metoprolol Pharmacokinetic Parameters	Day 1 Mean ± SD (n = 18)	Day 31 Mean ± SD (n = 17)	%GMR (90% CI)
C_{max} (ng/mL)	71.7 ± 30.4	141 ± 33.8	205.64 (172.77 - 244.77)
T_{max} (hr)	1.50 (0.75, 4.01)	2.00 (0.76, 3.00)	
$t_{½}$ (hr)	3.61 ± 0.99	6.61 ± 0.94	
AUC_{0-t} (ng*hr/mL)	397.80 ± 340.19	1242.36 ± 292.47	379.54 (299.61 - 480.78)
$AUC_{0-\infty}$ (ng*hr/mL)	411.30 ± 366.12	1410.83 ± 337.41	421.14 (332.72 - 533.07)

Day 1 = 1 metoprolol 50 mg IR tablet QD (fed)
Day 31 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID + 1 metoprolol 50 mg IR tablet QD (fed)
T_{max} presented as Median (Minimum, Maximum)
AUC_{0-t} represents area under the curve from time 0 to time of last quantifiable concentration, up to 24 hours postdose.
Parameters were ln-transformed prior to statistical analysis.
%GMR (% Geometric Mean Ratio) = 100*(test/reference)
90% CI = 90% Confidence Interval

Food Effect Comparisons:

Table 4 Statistical comparison for naltrexone PK parameters for High-fat, high-calorie meal (Day 33 or 34) versus Fasted (Day 33 or 34)

Pharmacokinetic Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals
	EFed	EFast		
Plasma Naltrexone				
C_{max} (ng/mL)	2.62	1.37	191.64	155.28 - 236.52
C_{min} (ng/mL)	0.14	0.16	88.39	69.26 - 112.80
AUC_{0-12} (ng*hr/mL)	11.19	6.58	169.97	150.53 - 191.92
Plasma 6-Beta Naltrexol				
C_{max} (ng/mL)	52.62	43.39	121.26	110.53 - 133.04
C_{min} (ng/mL)	20.04	20.50	97.72	87.44 - 109.20
AUC_{0-12} (ng*hr/mL)	400.57	379.77	105.48	98.21 - 113.29

Treatment EFed: Morning dose of 2 naltrexone SR 8 mg/bupropion 90 mg SR combination trilayer tablets (fed) (Day 33 or 34) (Test)
Treatment EFast = Morning dose of 2 naltrexone SR 8 mg/bupropion 90 mg SR combination trilayer tablets (fasted) (Day 33 or 34) (Reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

Table 5 Statistical comparison for naltrexone PK parameters for Moderate-fat, moderate-calorie meal (Day 30) versus Fasted (Day 33 or 34)

Pharmacokinetic Parameter	Geometric LS Means -- D24 (PK Day 30)	Geometric LS Means -- EFast	% Geometric Mean Ratio	90% Confidence Intervals
Plasma Naltrexone				
C_{max} (ng/mL)	2.48	1.37	180.53	154.76 - 210.61
C_{min} (ng/mL)	0.17	0.16	110.04	89.98 - 134.57
AUC_{0-12} (ng*hr/mL)	11.16	6.58	169.70	155.90 - 184.73
Plasma 6-Beta Naltrexol				
C_{max} (ng/mL)	49.96	43.48	114.91	107.05 - 123.35
C_{min} (ng/mL)	22.39	20.57	108.85	99.54 - 119.04
AUC_{0-12} (ng*hr/mL)	402.88	380.06	106.00	99.99 - 112.38

Treatment EFast = Morning dose of 2 naltrexone SR 8 mg/bupropion 90 mg SR combination trilayer tablets (fasted) (Day 33 or 34) (Reference)
PK Day 30 = Treatment D24 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID (fed) (Test)

Table 6 Statistical comparisons for naltrexone PK parameters for High-fat, high-calorie meal (Day 33 or 34) versus Moderate-Fat, moderate calorie meal (Day 30)

Pharmacokinetic Parameter	Geometric LS Means EFed	Geometric LS Means D24 (PK Day 30)	% Geometric Mean Ratio	90% Confidence Intervals
Plasma Naltrexone				
C_{max} (ng/mL)	2.61	2.48	105.17	90.15 - 122.69
C_{min} (ng/mL)	0.14	0.17	80.15	65.54 - 98.02
AUC_{0-12} (ng*hr/mL)	11.18	11.16	100.20	92.04 - 109.07
Plasma 6-Beta Naltrexol				
C_{max} (ng/mL)	52.51	49.96	105.10	97.91 - 112.81
C_{min} (ng/mL)	19.95	22.39	89.09	81.47 - 97.42
AUC_{0-12} (ng*hr/mL)	400.91	402.88	99.51	93.86 - 105.50

PK Day 30 = Treatment D24 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID (fed) (Reference)
Treatment EFed: Morning dose of 2 naltrexone SR 8 mg/bupropion 90 mg SR combination trilayer tablets (fed) (Day 33 or 34) (Test)

Table 7 Statistical comparison for bupropion PK parameters for High-fat, high-calorie meal (Day 33 or 34) versus Fasted (Day 33 or 34)

Pharmacokinetic Parameter	Geometric LS Means EFed	Geometric LS Means EFast	% Geometric Mean Ratio	90% Confidence Intervals
Plasma Bupropion				
C_{max} (ng/mL)	164.11	128.24	127.97	118.72 - 137.95
C_{min} (ng/mL)	37.85	40.79	92.79	88.12 - 97.70
AUC_{0-12} (ng*hr/mL)	1060.19	947.12	111.94	107.31 - 116.77
Plasma Hydroxybupropion				
C_{max} (ng/mL)	1514.19	1511.10	100.20	96.56 - 103.99
C_{min} (ng/mL)	1176.55	1146.70	102.60	98.78 - 106.58
AUC_{0-12} (ng*hr/mL)	16270.68	16260.62	100.06	97.37 - 102.83
Plasma Threohydrobupropion				
C_{max} (ng/mL)	677.93	622.71	108.87	104.69 - 113.22
C_{min} (ng/mL)	506.42	485.45	104.32	100.90 - 107.85
AUC_{0-12} (ng*hr/mL)	7143.28	6795.33	105.12	102.12 - 108.21
Plasma Erythrohydrobupropion				
C_{max} (ng/mL)	138.48	131.90	104.99	102.07 - 107.98
C_{min} (ng/mL)	109.67	105.72	103.73	100.80 - 106.75
AUC_{0-12} (ng*hr/mL)	1498.19	1443.17	103.81	101.11 - 106.58

Table 5 Statistical comparison for bupropion PK parameters for Moderate-fat, moderate-calorie meal (Day 30) versus Fasted (Day 33 or 34)

Pharmacokinetic Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals
	D24 (PK Day 30)	EFast		
Plasma Bupropion				
C_{max} (ng/mL)	149.87	127.88	117.20	107.95 - 127.25
C_{min} (ng/mL)	38.52	40.66	94.73	89.52 - 100.25
AUC_{0-12} (ng*hr/mL)	1035.79	944.22	109.70	104.74 - 114.89
Plasma Hydroxybupropion				
C_{max} (ng/mL)	1632.58	1513.42	107.87	102.89 - 113.09
C_{min} (ng/mL)	1302.69	1145.40	113.73	108.22 - 119.53
AUC_{0-12} (ng*hr/mL)	17418.76	16264.63	107.10	102.88 - 111.49
Plasma Threohydrobupropion				
C_{max} (ng/mL)	692.70	623.48	111.10	106.05 - 116.39
C_{min} (ng/mL)	521.58	485.46	107.44	102.68 - 112.43
AUC_{0-12} (ng*hr/mL)	7304.37	6793.58	107.52	103.20 - 112.01
Plasma Erythrohydrobupropion				
C_{max} (ng/mL)	142.68	132.08	108.03	103.29 - 112.97
C_{min} (ng/mL)	114.90	105.67	108.73	103.68 - 114.04
AUC_{0-12} (ng*hr/mL)	1544.63	1443.35	107.02	102.68 - 111.53

Table 6 Statistical comparison for bupropion PK parameters for High-fat, high-calorie meal (Day 33 or 34) versus Moderate-Fat, moderate calorie meal (Day 30)

Pharmacokinetic Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals
	EFed	D24 (PK Day 30)		
Plasma Bupropion				
C_{max} (ng/mL)	164.07	149.87	109.47	100.83 - 118.86
C_{min} (ng/mL)	37.94	38.52	98.51	93.09 - 104.24
AUC_{0-12} (ng*hr/mL)	1061.98	1035.79	102.53	97.90 - 107.38
Plasma Hydroxybupropion				
C_{max} (ng/mL)	1514.35	1632.58	92.76	88.48 - 97.25
C_{min} (ng/mL)	1179.27	1302.69	90.53	86.14 - 95.14
AUC_{0-12} (ng*hr/mL)	16293.09	17418.76	93.54	89.85 - 97.37
Plasma Threohydrobupropion				
C_{max} (ng/mL)	678.78	692.70	97.99	93.54 - 102.66
C_{min} (ng/mL)	507.37	521.58	97.27	92.96 - 101.79
AUC_{0-12} (ng*hr/mL)	7160.65	7304.37	98.03	94.10 - 102.13
Plasma Erythrohydrobupropion				
C_{max} (ng/mL)	138.66	142.68	97.18	92.93 - 101.63
C_{min} (ng/mL)	109.85	114.90	95.60	91.16 - 100.27
AUC_{0-12} (ng*hr/mL)	1501.18	1544.63	97.19	93.25 - 101.29

Sponsor's Conclusions:

- Steady-state dosing of 2 naltrexone 8 mg sustained release (SR)/bupropion 90 mg SR combination trilayer tablets given twice daily had a significant effect on the single-dose plasma PK of metoprolol (50 mg) under fed conditions in healthy adult subjects genotyped as CYP2D6 extensive metabolizers. As expected, the GMRs for the comparison of metoprolol C_{max} and $AUC_{0-\infty}$ parameter values between the metoprolol alone and naltrexone SR/ bupropion SR + metoprolol treatments were 206% and 421%, respectively.
- Based on the comparison of naltrexone exposure following single and multiple (steady-state) doses of naltrexone SR/bupropion SR combination trilayer tablets in fed condition, naltrexone exhibited linear, time invariant PK (90% CI of AUC GMR ratio contained within 80 -125% range), with negligible accumulation (about 7%) at steady state, which was consistent with mean $t_{½}$ of approximately 4 hours and the twice daily dosing frequency.
- Dose adjusted accumulation of bupropion at steady state from the administration of naltrexone SR/bupropion SR combination trilayer tablets twice daily with food was approximately 30%, which was predicted by the 11 hour $t_{½}$ of bupropion measured in the first 24 hours following single dose.
- Absence of drug interaction effect in presence of metoprolol was demonstrated for bupropion but not for naltrexone: co-administration of single-dose metoprolol with naltrexone SR/bupropion SR at steady state had no effect on bupropion PK (90% CIs for comparison of C_{max}, C_{min}, and AUC_{0-12} GMRs within 80-125%), but mean naltrexone C_{max}, C_{min}, and AUC_{0-12} parameter values were approximately 29%, 17% and 25% lower, respectively relative to when naltrexone SR/bupropion SR was administered alone at steady state. These slight reductions in naltrexone exposure are unlikely to be clinically meaningful.
- Administration of naltrexone SR/bupropion SR following moderate-fat, moderate-calorie meal and following high-fat, high-calorie meal resulted in, respectively, 81% and 92%, higher naltrexone C_{max} values and 70% higher (for both prandial states) AUC_{0-12} values relative to administration under fasting conditions. Relative to fasting state, food (moderate-fat, moderate-calorie meal or high-fat, high-calorie meal) had no effect on bupropion C_{min} and AUC_{0-12} values, and resulted in minor increases in bupropion C_{max} of 117% for moderate-fat, moderate-calorie versus fasted treatment comparison, and 128% for the high-fat, high-calorie versus fasted treatment comparison.
- Changing the meal composition prior to the morning dose from moderate-fat, moderate-calorie meal to high-fat, high-calorie meal had no apparent effect on bupropion absorption from the trilayer tablet formulation, and only negligible effect on naltrexone C_{max} and AUC_{0-12} parameter values, with the GMRs and CIs for the comparison contained within 80% - 125% bioequivalence range.

Overall, sponsor's conclusions from this study are reasonable and acceptable with the following exceptions:

- The food effect evaluation is limited by the fact that the dosing with changed diet pattern at steady-state (fasting or fed) was single and did not proceed to attain the stead-state. The effect of high-fat diet or fasting was inconsistent on the two occasions (Day 33 and 34) and cannot be explained.
- The food-effect results are however useful in understanding the nature of variability in exposure of naltrexone, bupropion, and metabolites resulting from change in conditions under which Contrave is administered.

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/s/

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CLINICAL PHARMACOLOGY REVIEW

NDA: 200063	Submission Date(s): 03/31/2010
Brand Name	CONTRAVE®
Generic Name	Naltrexone Hydrochloride and Bupropion Hydrochloride in combination
Clinical Pharmacology Reviewer	Manoj Khurana, Ph.D.
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Primary Pharmacogenomics Reviewer	Michael Pacanowski, Pharm.D., M.P.H.
OCP Division Director	Chandrahas Sahajwalla, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Orexigen Therapeutics
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Sustained-release trilayer tablets for oral administration, Naltrexone/Bupropion 4/90 mg and 8/90 mg
Proposed Indication	Treatment of obesity and weight management, including weight loss and maintenance of weight loss, to be used in conjunction with lifestyle modification.

List of Figures and Tables

1 Executive Summary

Orexigen Therapeutics (the Sponsor) is seeking an approval of CONTRAVE® (hereafter Contrave or NB) (b) (4) Tablets for the treatment of obesity and weight management. Contrave is a fixed-dose combination drug product containing two active pharmaceutical ingredients, naltrexone hydrochloride (hereafter naltrexone or N**)** and bupropion hydrochloride **(**hereafter bupropion or B). Naltrexone is a μ (mu) opioid antagonist and bupropion is a dopamine (DA) and norepinephrine (NE) reuptake inhibitor.

Since both active ingredients are approved in the US for use in other indications, this application is submitted by the sponsor as a 505(b)(2) NDA. The sponsor has referenced pertinent information from approved US prescribing information for ReVia® (naltrexone hydrochloride; NDA 18-932) and Wellbutrin SR® (bupropion hydrochloride; NDA 20-358).

Each Contrave tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and claimed to be a (b) (4) tablet. A rapidly dissolving inert layer separates the two drug layers. Contrave will be available as two naltrexone dosage strength tablets:

- CONTRAVE® 8/90, (naltrexone HCL 8 mg/bupropion HCL 90 mg) tablets (hereafter NB 8/90 mg)
- CONTRAVE® 4/90, (naltrexone HCL 4 mg/bupropion HCL 90 mg) tablets (hereafter NB 4/90 mg)

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted in support of NDA 200063 for CONTRAVE® and found them acceptable.

1.2 Post-marketing Requirements

In vitro study results that showed Contrave is an Organic Cation Transporter 2 (OCT2) inhibitor should be confirmed through an in vivo study. Therefore, the sponsor should conduct the in vivo drug-drug interaction study evaluating the impact of Contrave on a OCT2 substrate such as metformin.

1.3 Summary of Important Clinical Pharmacology Findings

Sponsor is seeking the following indication for Contrave: "*Contrave is indicated for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification. Contrave is recommended for patients with an initial body mass index ≥30 kg/m^2 or ≥27 kg/m^2 with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension)*". The Contrave clinical development program is composed of 23 trials, including 15 Phase 1, four Phase 2, and four pivotal Phase 3 studies. Clinical Pharmacology review of the information submitted by the sponsor, in support of their application, revealed the following important findings:

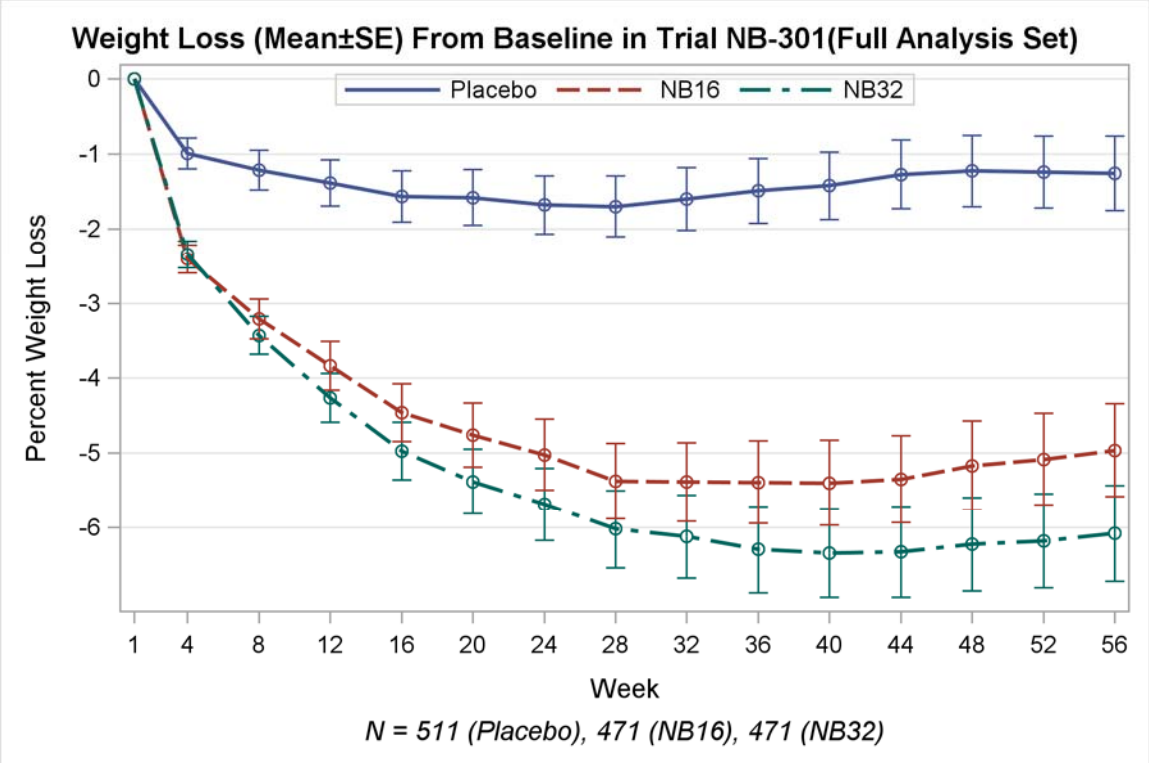
Dose/Exposure-Response for Weight loss (Efficacy):

Sponsor proposed a recommended daily dose of two NB 8/90 mg tablets twice daily (BID), which sums up to a total daily dose of 32 mg naltrexone/360 mg bupropion. The adequacy of the proposed dosage regimen was evaluated from the dose-response relationship.

Longitudinal (over time) and cross-sectional (across treatments) weight-loss data from the placebo-controlled Phase 3 Trial NB-301 was used for this purpose. Among the four Phase 3 trials, NB-301 is the only trial that tested two daily dose levels of Contrave: 16 mg naltrexone/360 mg bupropion (NB16**)** and 32 mg naltrexone/360 mg bupropion **(**NB32**)** over 56 week duration. Trials NB-302, NB-303, and NB-304 tested NB32 versus placebo. Additionally, NB-303 trial tested a higher 48 mg naltrexone/360 mg bupropion (NB48) dose in subjects who did not respond to NB32 by week 28. NB48 dose was given using 2 x NB 12/90 mg tablet BID, which is not proposed for approval under this application.

The percent weight loss versus time profile from Phase 3 trial NB-301 shows a dose-dependent reduction in weight. The data also showed that the maximal mean percent reduction in weight from baseline is achieved after week 28 in both low (NB16) and high dose (NB32) treatment arms (Figure 1).

Figure 1 Time course of percent weight loss from baseline in the 56-week Phase 3 confirmatory trial (NB-301)



In addition, dose-response data from the efficacy trial NB-301 showed that NB32 dose was numerically beneficial for placebo-corrected weight-loss over NB16 dose.

According to the FDA Guidance document 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-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*
- *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant"*.

Notably, the efficacy for Contrave was marginal as none of Phase 3 trials achieved the mean placebo corrected weight loss of 5%, and thus did not satisfy the first of the two efficacy benchmarks recommended in the Guidance. With regards to dose-response, NB-301 trial results showed that the placebo corrected mean weight loss was <5% not meeting the efficacy benchmark; mean (95% CIs) of -3.67% (-4.5, -2.85) for NB16 and mean (95% CIs) of -4.81% (-5.63, -3.99) for NB32, respectively.

NB32 dose satisfied the second efficacy benchmark criteria in two adequately designed 56 week trials (NB-301 and NB-304) among the four Phase 3 trials. From a dose-response perspective, both NB16 and NB32 doses evaluated in 56 week trial NB-301 satisfied the second efficacy benchmark criteria as the proportion of patients loosing weight was at least 35%, double the proportion in placebo, and the difference was statistically significant. However, numerical benefit of NB32 over NB16 was also evident based on a greater percentage of subjects loosing >5% weight with NB32 against NB16 and placebo.

Therefore, the recommended daily dose of NB32 is acceptable from dose-response perspective and with regards to the maximum weight loss benefit offered by this dose.

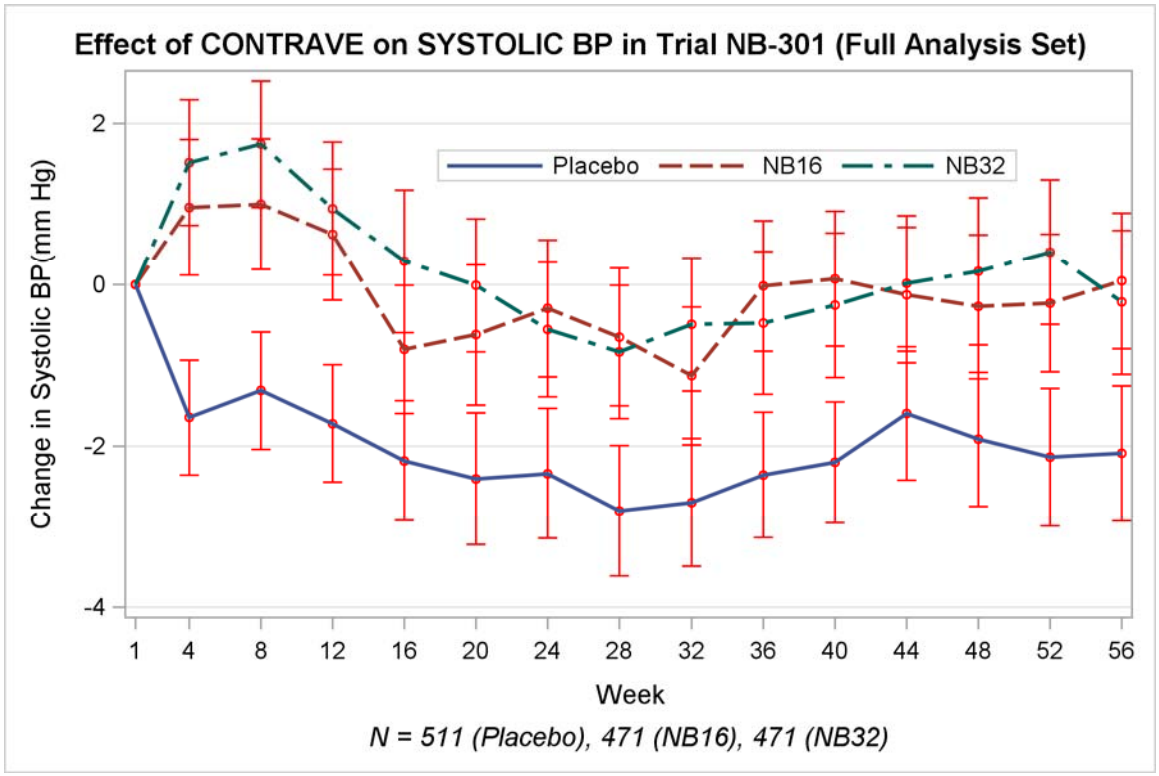
Systemic exposure-response analysis from the PK data collected in Phase 3 Trial NB-303 showed a shallow exposure-weight loss relationship for increasing bupropion trough concentrations. The observed bupropion trough concentrations were also associated with maximal weight loss achieved in this trial. This analysis was also explored with the pharmacological activity weighted composite (PAWC) metric (see QBR Section 2.2.1 for details), which was computed as the sum of parent and metabolite nanomolar (nM) concentrations for naltrexone and its metabolite 6β-naltrexol, and bupropion and its metabolites, without applying any potency factors (Agency's analysis did not use the potencies as they are based on animal experiments and their relevance to weight loss in humans is unknown). Similar shallow trend was observed for the PAWC-weight loss relationship. However, it was noted that the weight loss from the PK subset, whose PK samples were utilized in evaluation of the exposure-weight loss and PAWC-weight loss relationships, was not representative of that of the whole population in Trial NB-303, as the weight loss was greater in PK subset versus subjects with no PK collection. This could likely be due to the higher proportion of drop-outs observed in the group without PK sampling versus the group with PK sampling, as subjects had to remain in the trial in order to provide the week 28 to week 56 PK samples . In this reviewer's opinion subjects who stay in the trial tend to have better efficacy and less safety

Dose/Exposure-Response for Safety:

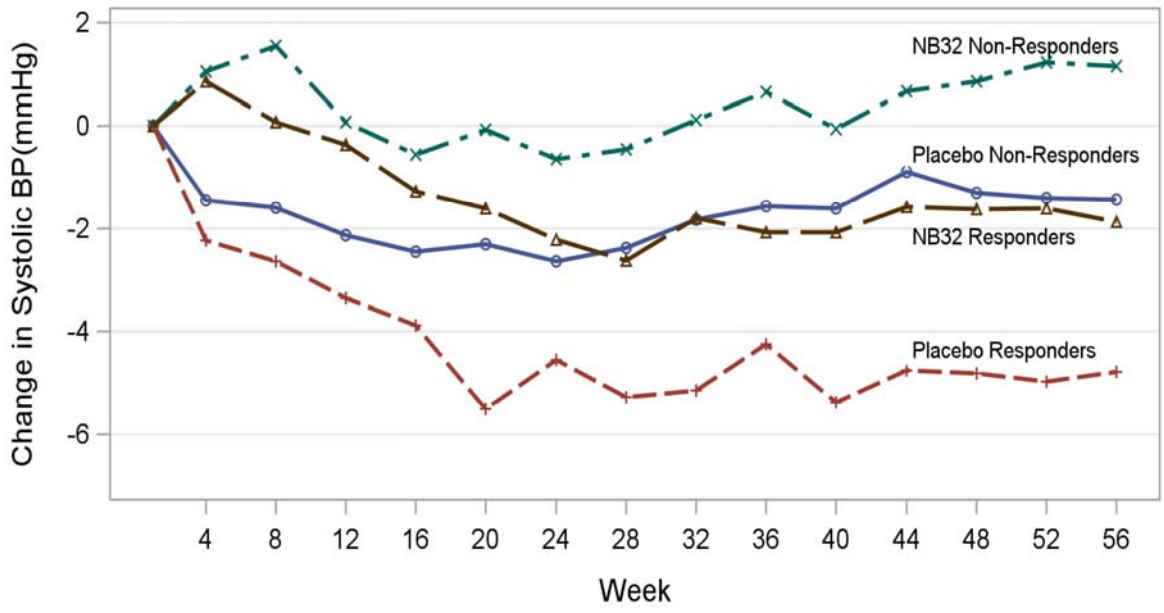
Effect on Blood Pressure: Bupropion is known to increase the blood pressure through unknown mechanism. Contrave treatment was also associated with an increase in systolic blood pressure (SBP) in obese patients. Data from placebo controlled Trial NB-301, which tested two dose levels of the combination (bupropion dose was same 360 mg/day), showed that the maximum mean increase of around 1 to 2 mm Hg from baseline was observed up to Visit 8 with the active treatment arms. This mean rise in SBP returned to baseline by week 16. The placebo group showed greater reduction in SBP from baseline (Figure 2a). When evaluated based on 5%

responder status by treatment (patients loosing ≥5% weight from baseline) in the completer population, the placebo responders had considerable improvement in blood pressure. Whereas, NB32 non-responder had their blood pressure elevated over the baseline and NB32 responders did not have any improvement in blood pressure (Figure 2b) Therefore, the beneficial effect of weight loss in terms of reduction in SBP was absent in the Contrave treatment group.

Figure 2 (a) Time course of systolic blood pressure change from baseline in the 56-week Phase 3 confirmatory trial (NB-301), (b) Mean change in systolic blood pressure from baseline by treatment response group (Completers) for NB32 pooled Phase 3 data



(b)



The maximum risk with regards to the increase from baseline in SBP among top 5% of patients who had increase in SBP from baseline, as determined from the cumulative distribution of patients versus change from baseline in SBP, ranges from 2 to 5 mm Hg for Contrave treatment against that of placebo.

Systolic blood-pressure changes did not show any trend when the mean changes from baseline were evaluated against increasing bupropion exposures (See PM review, Section 1.1.3 for details in Appendix 4.2).

Exposure-AE: Most commonly reported treatment emergent adverse event (TEAEs) with Contrave was nausea. Constipation, vomiting, dry mouth, diarrhea, headache, and insomnia were other TEAEs from Contrave treatment. Safety data from NB-301 revealed that frequency (% subjects with AE) of nausea was higher in both NB16 (27.2%) and NB32 (29.8%) dose groups, when compared against placebo. There was slight increase in frequency of vomiting (6.3% to 9.8%), dizziness (7.7% to 9.4%), insomnia (6.3% to 7.5%), and hot flushes (2.3% to 5.2%) with increase in dose from NB16 to NB32. Percentage of subjects reporting constipation, dry mouth, diarrhea, and headache were similar for the two dose groups, and overall comparable to placebo. Exposure-response analysis from Trial NB-303 showed that percentage of subjects reporting nausea and vomiting increased with increasing bupropion concentrations. However, no such relationship was apparent with naltrexone concentrations. Nausea and vomiting have been associated separately with the use of bupropion or naltrexone. The other adverse events such as constipation, insomnia, anxiety did not show any relationship to either naltrexone or bupropion exposure.

QT/QTc: A thorough QT study was not conducted for Contrave. According to the Inter-disciplinary Review Team (IRT) Review, large changes in QTc intervals were not observed in studies NB-228 and NB-303. However, the trial design was not sufficient to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance.

Effect on Serum Creatinine: The clinical trial data showed an increase in serum creatinine from baseline in the Contrave treated patients. To explain the plausible mechanism, the sponsor provided an in vitro DDI study report. This in vitro study was conducted to evaluate the ability of bupropion and its metabolites or naltrexone and its metabolite, to inhibit organic cation transporter, OCT2 in the kidney. OCT2 is involved in tubular secretion of creatinine and other drugs such as metformin. The in vitro study results demonstrated that bupropion and its metabolites, specifically threohydrobupropion and erythrohydrobupropion can inhibit OCT2 at the exposure equivalent to combined Cmax at steady state. According to the International Transporter Consortium recommendations[1], if the ratio of free therapeutic concentration to the IC50 is greater than 0.1, the inhibition potential is considered to be clinical relevant. In this case, this ratio is 0.29. Thus, slight increase in serum creatinine noted in the Phase 3 trials could be due to the OCT2 inhibition. In addition, these in vitro findings should be confirmed in an in vivo study to establish the OCT2 inhibitory effects of bupropion and its metabolites. Since this has implications on drug interactions via this transporter pathway, sponsor should address the in vivo DDI potential of Contrave with OCT2 substrates such as metformin. In addition, sponsor should also evaluate the effect of Contrave administration on glomerular filtration rate to establish that the serum creatinine increase is not due to any untoward effect of bupropion on the renal function.

[1] Membrane Transporters in Drug Development. Nature Reviews Drug Discovery 9, 215-236, 2010.

General ADME:

Naltrexone: The existing clinical pharmacology data on naltrexone demonstrate that upon oral administration, naltrexone undergoes high first pass metabolism to form 6β-naltrexol in humans via non-CYP mediated mechanism. Both the parent and the metabolite are subject to conjugation prior to renal excretion. Renal clearance of 6β-naltrexol also involves active tubular secretion.

In the current application, naltrexone exhibited approximately dose proportional increase in exposure from the two Contrave dose strengths; NB 4/90 mg and NB 8/90 mg when given orally as two tablets of NB 4/90 mg and NB 8/90 mg. After the single oral dose of Contrave, naltrexone plasma concentrations declined with elimination t1/2 of 5 hr and the concentrations of 6β-naltrexol declined in a bi-exponential fashion with a relatively longer t1/2 of 13 hr, suggesting its peripheral distribution. The exposure to 6β-naltrexol was numerically higher than naltrexone from Contrave. After single oral dose of 1 x NB 8/90 mg, for 6β-naltrexol, the area under concentration time curve (AUC) and the maximum concentration (Cmax) were approximately 30- and 15-fold greater than that for naltrexone, respectively. At steady-state 6β-naltrexol, AUC and Cmax were approximately 45- and 25-fold greater than that for naltrexone, respectively. Accumulation of 6β-naltrexol was greater than expected (~300%) from t1/2 of 13 hr and BID administration. Although, the involvement of transporters in tubular secretion of 6β-naltrexol is unclear, based on the findings that bupropion and its metabolite inhibit organic cation transporter, this greater than expected accumulation could be due to an unidentified mutual interaction between the two Contrave components.

Bupropion: The existing clinical pharmacology data on bupropion demonstrate that upon oral administration, bupropion is subjected to extensive first pass metabolism primarily by CYP2B6 to form major metabolite hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of other two major metabolites threohydrobupropion or erythrohydrobupropion.

In the current application, bupropion pharmacokinetic profile was similar from the two Contrave dose strengths; NB 4/90 mg and NB 8/90 mg when given orally as two tablets each of NB 4/90 mg and NB 8/90 mg, respectively (bupropion dose was same). After single oral dose of Contrave, bupropion plasma concentrations declined with elimination half-life of 21 hr in a biexponential fashion, suggesting its peripheral distribution. Hydroxybupropion, threohydrobupropion, and erythrohydrobupropion plasma concentrations declined with t1/2 of ~27, 47, and 32 hr, respectively. The AUC for hydroxybupropion and threohydrobupropion after single Contrave dose of NB 8/90 mg was 12-fold and 4-fold higher, respectively, than bupropion AUC. Both Cmax and AUC for hydroxybupropion and threohydrobupropion at steady state were substantially higher than bupropion values. Whereas, slightly higher AUC was observed for erythrohydrobupropion relative to the parent drug, after single as well as multiple twice-daily doses.

Thus, naltrexone, bupropion, and their metabolites accumulate at steady-state.

Intrinsic Factors (Body weight, Age, BMI, Gender, Race, and Genetics etc.) Affecting Exposure:

The population pharmacokinetic analysis was conducted separately for each of the 6 analytes: bupropion, hydroxybupropion, erythrohydrobupropion, threohydrobupropion, naltrexone, and 6β-naltrexol. The effects of various covariates e.g. ideal body weight, actual body weight, age, BMI, gender, and race on naltrexone and bupropion PK parameters were evaluated in this analysis. Naltrexone CL/F in non-whites was 34% lower than that of white subjects. However, this effect was not clinically meaningful. There was no difference in 6β-naltrexol CL/F among non-whites

and whites. Effects of other covariates such as ideal body weight, weight, age and gender on the naltrexone PK could not be established with precision due to limitations of the data.

Ideal body weight and gender were identified as significant covariates for the bupropion CL/F but the effect of these covariates was not clinically meaningful to warrant any dose adjustments. CYP2B6 gene variants may account for only a small proportion of the overall variability in bupropion or hydroxybupropion exposure based on the observed inter-individual variability, absence of marked race effects, and published pharmacogenetic studies (see Appendix 4.3 for details). Overall, these findings, therefore, do not warrant for any dose-adjustments of Contrave based on any of these covariates.

Elderly patients: Contrave clinical program provided limited safety and efficacy information on patients above 65 years of age. PK of Contrave was not evaluated in the elderly subjects. Although age was not a significant covariate for clearance of naltrexone, bupropion and their metabolites, the finding is confounded by the known decrease in renal function with age. Therefore, the metabolites of naltrexone and bupropion are expected to accumulate to a greater extent in elderly than young adults. Therefore, considering the sustained serum creatinine increase (OCT2 inhibition due to bupropion and metabolites) and blood pressure effects observed due to Contrave, in elderly population Contrave should be used with caution and their serum creatinine should be monitored. The long term cardiovascular safety of Contrave should also be evaluated in this subpopulation.

Renal Impairment: Naltrexone, 6β-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion and their conjugates are excreted in urine. Renal clearance of 6β-naltrexol also involves active tubular secretion. Adequate studies of naltrexone in patients with severe renal impairment have not been conducted. Based on the bupropion product labels, there is limited information on the pharmacokinetics of bupropion in patients with renal impairment, though one study showed that moderate to severe renal impairment patients (GFR 30.9 ± 10.8 mL/min) about 2-fold higher exposures of bupropion were observed.

Population PK analysis of data from NB-303 trial revealed that apparent bupropion and naltrexone clearances were not influenced by creatinine clearance over the range of 53 mL/min to 150 mL/min (upper limit in Pop-PK analysis). Creatinine clearance was also linearly correlated with ideal body weight in this population. Ideal body weight adjusted apparent clearance of hydroxybupropion, threohydrobupropion, and erythrobupropion showed a shallow increase with increasing creatinine clearance. The ideal body weight adjusted clearance showed linear increase for 6β-naltrexol with increasing creatinine clearance. This suggests that with decreasing renal function these metabolites accumulate to relatively greater extent in comparison to that under normal renal function. Since there is limited information on relationship of metabolites with safety over the long-term use, Contrave should be used with caution in mild renal impairment subjects. The chronic Contrave use is associated with an increase in serum creatinine likely via inhibition of tubular secretion, which is preserved to certain extent in severe renal impairment.

Therefore, considering the known seizure risk profile of bupropion, the lack of BP benefit from weight loss, ~2-fold higher exposures of bupropion (>1.5 threshold), Contrave should (b) (4)

(b) (4)

Hepatic Impairment: There are no studies conducted for Contrave in hepatic impairment subjects. Naltrexone is metabolized to 6β-naltrexol (non-CYP mediated pathway), and bupropion

is metabolized to hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Both parent drugs and their metabolites undergo conjugation in liver. Adequate studies of naltrexone in patients with hepatic impairment have not been conducted. Based on the bupropion product labels, there is lack of systematic evaluation of bupropion in hepatic impaired. However, the available data suggests that bupropion exposure could be higher (3-fold higher AUC in severe hepatic cirrhosis) and metabolites also had increased exposures in comparison to healthy subjects. Therefore, Contrave use requires caution in mild and moderate hepatic impairment and (b) (4)

Extrinsic Factors:

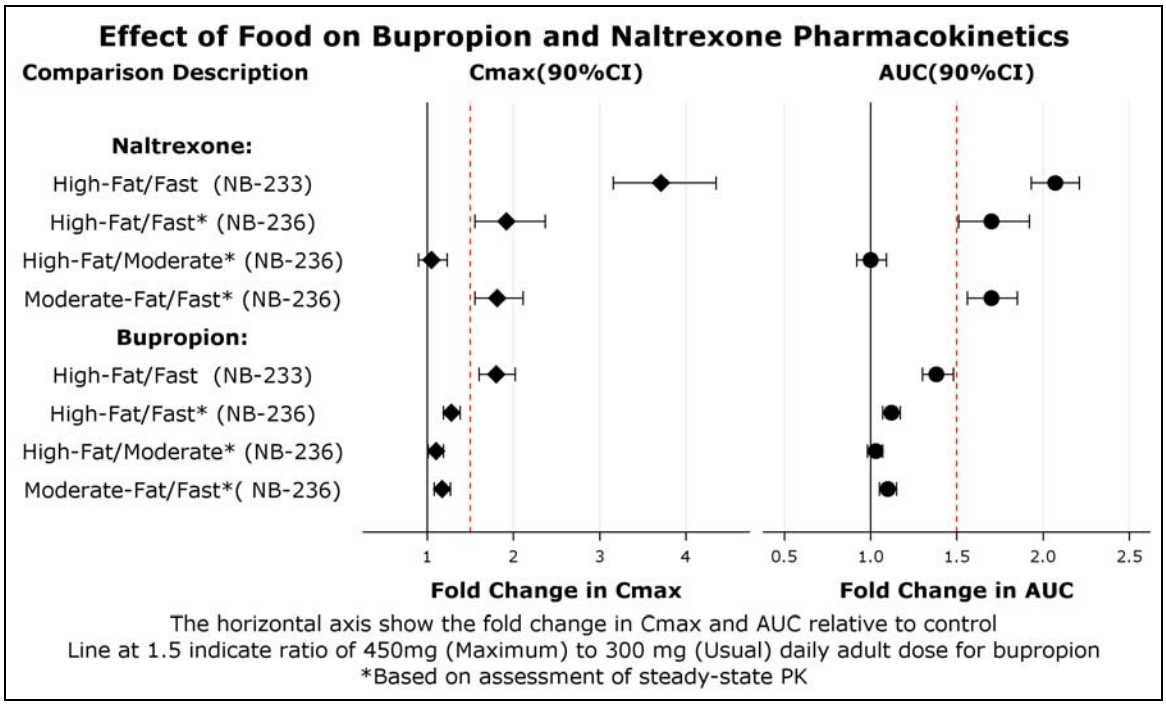
Food Effect: The safety concerns for abrupt increase in seizure frequency above 450 mg total daily bupropion SR dose (1.5 fold higher in dose when compared to 300 mg total daily dose) are well established. Since the bupropion exposure from Contrave (bupropion dose 180 mg; given as 2 x NB 8/90 mg tablet) is comparable to single bupropion SR 150 mg dose, same threshold of fold-increase greater than 1.5 can be considered clinically alarming for Contrave. Single oral dose food effect study showed that when given with high-fat meal, naltrexone peak and total exposure increased to 4-fold and 2-fold, respectively in comparison to those under the fasted state. This increase in exposure numerically exceeded those expected from usual 50 mg daily dose of naltrexone IR (~1.5-fold when compared to 32 mg). Bupropion peak and total exposure were increased in clinically significant way in the presence of high-fat meal with fold increase in Cmax greater than 1.5 (See Figure 3).

Steady-state food effect showed similar direction but lower magnitude than the single dose study. However, the study design and results were not sensitive to rule out the high-fat food effect.

Food effect is unknown for the existing naltrexone IR formulation. Bupropion SR (Wellbutrin SR label) documents that food increased Cmax and AUC of bupropion by 11% and 17%, respectively, which was not considered as clinically significant food effect. Therefore, the food effect that was seen in this application is unique to the Contrave formulation.

Considering the seizure risk profile of bupropion, from clinical pharmacology perspective Contrave should not be taken with high-fat meal.

Figure 3 Effect of food on naltrexone and bupropion pharmacokinetics



Effect of Contrave on Co-administered Drugs:

Drug-drug interaction (DDI) studies in the Contrave development program were not conducted with the primary objective of evaluating the effect of Contrave on the pharmacokinetics of co-administered drugs (atorvastatin, valsartan, glyburide, nifedipine, lisinopril) except the study with metoprolol. The treatment arm of co-administered drug given alone was not included in any study except in the DDI study with metoprolol. All other studies compared the pharmacokinetic data collected after co-administration with Contrave to those reported in literature or in approved product labels. This cross-study comparison is acceptable for signal detection from clinical pharmacology perspective and cannot be relied upon for establishing or ruling out a DDI. The cross-study comparison do not signal for any meaningful changes in the exposure of the co-administered drugs due to Contrave; atorvastain, valsartan, glyburide, nifedipine, and lisinopril.

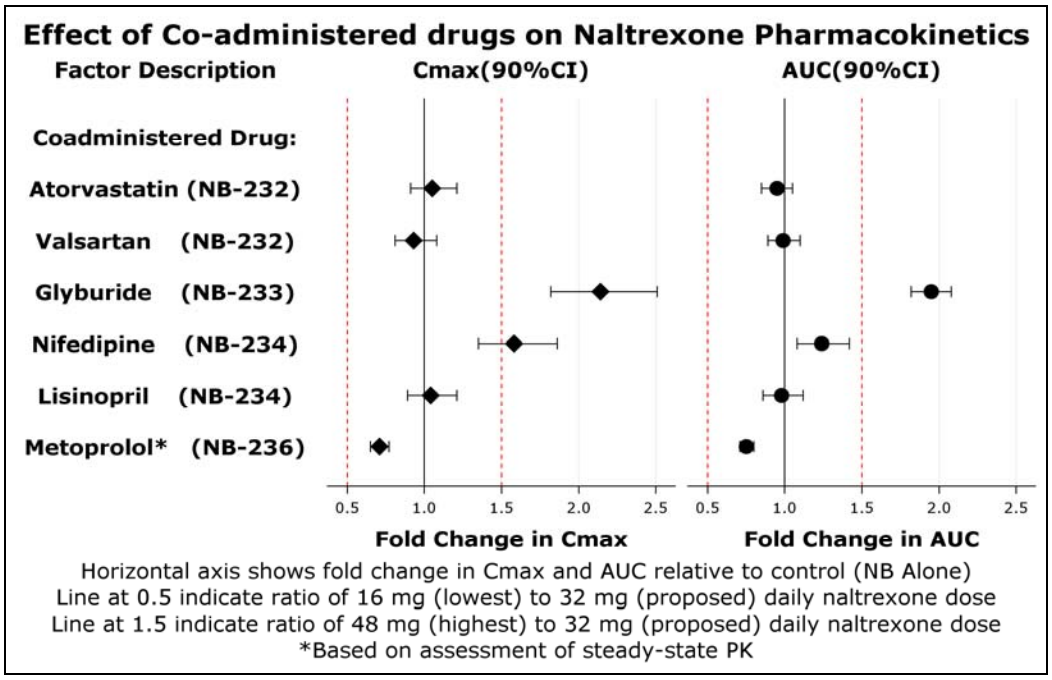
Co-administration of single metoprolol dose at steady-state of Contrave resulted in 2-fold (90% CI 1.73 – 2.45) increase in Cmax and 4-fold increase (90% CI 3.33 – 5.33) in AUC of metoprolol. This study was conducted in subjects genotyped as extensive CYP2D6 metabolizers to ensure that results are not confounded by the poor baseline metabolic capacity of poor metabolizers.

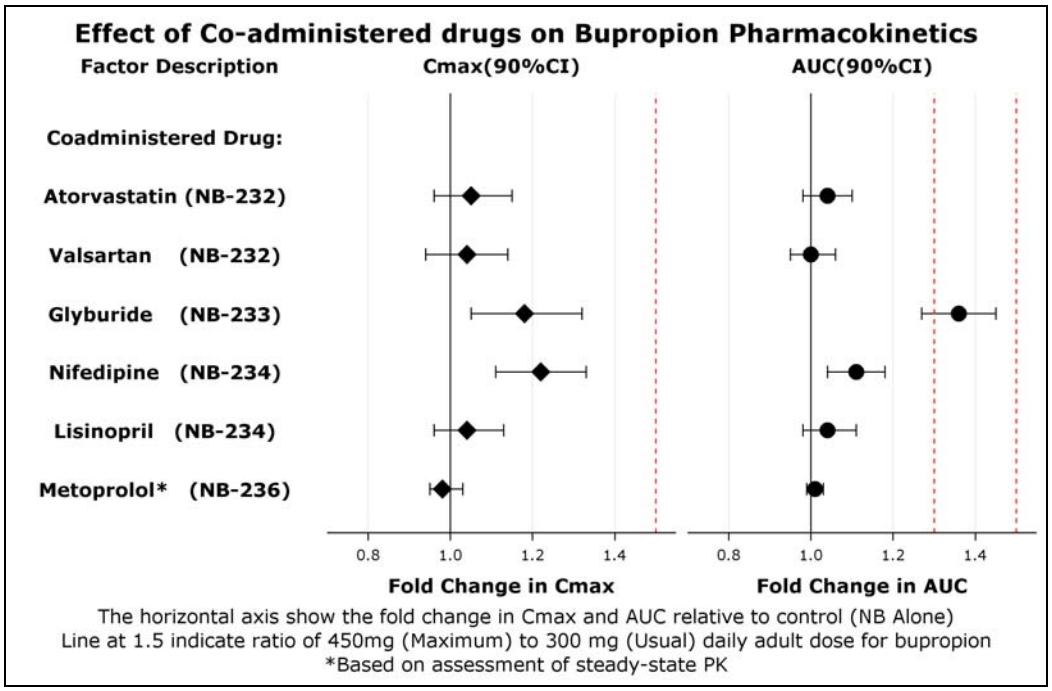
Based on these results, there is no need for Contrave dose adjustment with the co-administered drugs: atorvastatin, valsartan, glyburide, nifedipine, and lisinopril. Metoprolol and other CYP2D6 substrates need dose reduction and should be initiated at the lower end of their dose if co-administered with Contrave.

Effect of Co-administered Drugs on Contrave (Drug-drug Interactions):

Co-administration of various representative drugs did not affect the exposure of naltrexone or bupropion in a clinically meaningful way. The least square mean ratios were close to one and 90% confidence intervals were contained within the 0.8 to 1.25 interval. The results with glyburide were confounded with the food effect due to oral glucose solution that was co-administered. This food effect cannot be ruled out as the oral glucose solution is known to affect the gastro-intestinal motility.

Figure 4 Effect of co-administered drugs on naltrexone and bupropion pharmacokinetics.





PK Comparison of Intended Commercial vs. Phase 2/Developmental Formulations:

The tablet developed for use in Phase 3 and in key clinical pharmacology studies represents the intended commercial drug product (Manufactured under (b) (4)

The Contrave tablet was manufactured under (b) (4)

- (b) (4)
- (b) (4)

All pivotal Phase 3 studies (NB-301, NB-302, NB-303 and NB-304) as well as key clinical pharmacology studies of drug-drug interactions, of the effect of food, and those to evaluate the PK performance of developmental formulations against approved formulations (NB-230, NB-232, NB-233, NB-234 and NB-236) utilized the intended commercial formulation.

Bioanalytical Methodology:

For the clinical pharmacology assessments, naltrexone, 6β-naltrexol (major metabolite of Naltrexone), bupropion and its metabolite: hydroxybupropion, threohydrobupropion and erythrohydro (major metabolites) were quantitated in plasma using validated LC-MS/MS assay. The assay was validated for analyzing these 6 analytes in plasma samples in terms of recovery, range, accuracy, precision and sensitivity. The changes to the analytical sites or procedures were adequately supported by partial validation of methods whenever necessary.

2 Question Based Review

2.1 General Attributes

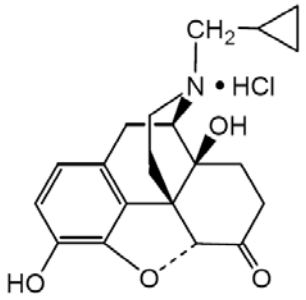
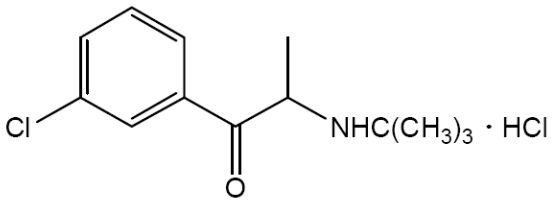
Orexigen Therapeutics is seeking the approval of combination product for the treatment of obesity, Contrave (naltrexone HCl and bupropion HCl) [redacted] (b) (4) Tablets. Naltrexone (Figure 5a) is an approved mu-opioid receptor antagonist indicated for the treatment of opiate and alcohol dependence, while bupropion (Figure 5b) is an approved norepinephrine and dopamine reuptake inhibitor indicated for the treatment of major depression and nicotine dependence.

Since both active ingredients are approved in the US for other indications, sponsor submitted a 505(b)(2) NDA, and referenced pertinent information from approved US prescribing information for ReVia® (naltrexone hydrochloride; NDA 18-932) and Wellbutrin SR® (bupropion hydrochloride; NDA 20-358).

The sponsor has supported the Contrave application with studies that compare different developmental and intended commercial drug product formulations, food effect, effect of co-administered drugs, and population pharmacokinetic analysis.

The chemical structures of naltrexone and bupropion are illustrated in Figure 5 below:

Figure 5 Chemical Structure of Naltrexone and Bupropion.

(a) Naltrexone	(b) Bupropion
	

Pharmacologically, the exact neurochemical appetite suppressant effects of Contrave are not fully understood. However, nonclinical studies suggest that Contrave has synergistic action on two distinct sites of the central nervous system that influence energy balance: the hypothalamus and the mesolimbic dopamine circuit (reward system). In nonclinical studies, bupropion has been shown to decrease food intake and increase energy expenditure, resulting in weight loss.

According to the proposed pharmacological mechanism of action, bupropion stimulates the activity of POMC cells in the hypothalamus, which are known to decrease food intake and increase energy expenditure. Activity of POMC cells is negatively auto-regulated by endogenous opioids, a compensatory mechanism that may limit sustained weight loss. Thus, naltrexone/bupropion in combination possibly acts as a dual POMC enhancer by stimulating activity of POMC and simultaneously antagonizing mu-opioid receptors on these same cells. By blocking opioid receptors on POMC cells, naltrexone could amplify the effect of bupropion. The mesolimbic dopamine system mediates reward-driven behavior, such as food-seeking and feeding. Nonclinical studies demonstrate that naltrexone and bupropion act synergistically in the reward system to decrease food intake.

Contrave is indicated for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification. Contrave is recommended for patients with an initial body mass index ≥30 kg/m^2 or ≥27 kg/m^2 with one or more risk factors (e.g., diabetes, dyslipidemia, or hypertension).

2.1.1 What are the proposed dosage regimens for Contrave?

The proposed Contrave tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and a more rapidly dissolving inert layer separating each drug. Contrave is available as two naltrexone dosage strength tablets:

- NB 8/90, (naltrexone HCL 8 mg/bupropion HCL 90 mg) [redacted] (b) (4) tablets
- NB 4/90, (naltrexone HCL 4 mg/bupropion HCL 90 mg) [redacted] (b) (4) tablets

The recommended dose of Contrave is two NB 8/90 tablets (Total dose of 16 mg naltrexone/180 mg bupropion) taken twice daily for a total daily dose of 32 mg naltrexone and 360 mg bupropion. Contrave dosing is initiated with once daily morning dose of NB 8/90 mg. The Contrave dose is escalated over a 3-week period until achieving the total daily maintenance dose of 32 mg naltrexone and 360 mg bupropion as shown in Figure 6 below. This is conceptually similar to the recommended usage of approved bupropion and naltrexone drug products, where doses of these two centrally acting compounds are slowly escalated to improve tolerability. The dose-escalation was used in the safety and efficacy evaluation for the two formulations as low (NB16) and high (NB32) total daily dose groups in trial NB-301 (Figures 6 and 7), and for the high total daily dose (NB32) in efficacy trials NB-302, NB-303, and NB-304.

Figure 6 Dose escalation for Contrave using NB 8/90 mg strength in Phase 3 trials.

Titration

AM Tablets:	1	1	2	2
	Week 1	Week 2	Week 3	Week 4
PM Tablets:	0	1	1	2
Total Daily N/B Dose (mg):	8/90	16/180	24/270	32/360

Figure 7 Dose escalation for Contrave using NB 4/90 mg strength in Trial NB-301.

Titration

AM Tablets:	1	1	2	2
	Week 1	Week 2	Week 3	Week 4
PM Tablets:	0	1	1	2
Total Daily N/B Dose (mg):	4/90	8/180	12/270	16/360

Although the recommended starting dose is NB 8/90 mg, sponsor proposed that treatment initiation and escalation with NB 4/90 tablets may be considered. If well tolerated, patients using NB 4/90 tablets should switch to NB 8/90 tablets to have their daily dose increased to the recommended maintenance daily dose of 32 mg naltrexone and 360 mg bupropion (two NB 8/90 tablets twice daily) to maximize weight loss. However, patients initiated with NB 8/90 tablets that experience treatment intolerance during the escalation or early maintenance period can be switched to NB 4/90 tablets.

The proposed total maximum daily dose of naltrexone (32 mg) is numerically lower than those used for other approved indications such as 50 mg once daily for treatment of alcohol dependence. The initial titration proposed for Contrave is conceptually similar to initiating naltrexone treatment with a lower dose of 25 mg in alcohol dependence.

The proposed total maximum daily dose of bupropion, 360 mg (180 mg BID) is numerically higher than the usual adult total daily dose of 300 mg (150 mg BID). The initial titration proposed for Contrave is conceptually similar to initiating bupropion treatment with a lower dose of 150 mg/day for WELLBUTRIN XL as a single daily dose in the morning, followed by increase to the 300-mg/day dose after 1 week. The usual adult target dose for WELLBUTRIN XL is 300 mg/day, given once daily in the morning. The usual adult target dose for Contrave is 180 mg BID regimen.

The two tablet strengths, NB 8/90 mg or NB 4/90 mg tablets, are designed to enable the titration regimen for both components during the first 3 weeks of treatment initiation.

2.1.2 What is the composition of the intended commercial Contrave formulation?

The details on the tablet composition and manufacturing should be referred to the CMC review. In brief, the proposed commercial presentations of naltrexone SR/bupropion SR tablets are composed of three layers. Two layers contain naltrexone and bupropion, respectively, which are separated by an inert layer. Both presentations of the intended commercial drug product (i.e. NB 4/90 mg and NB 8/90 mg) (b) (4) The composition of NB is listed in Table 1 below.

Table 1 Quantitative Composition of the NB 8/90 Tablet

Ingredient	Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet[a]	
(b) (4)				
Bupropion Hydrochloride USP	90.0		(b) (4)	Active ingredient
L-Cysteine Hydrochloride USP	(b) (4)			(b) (4)
Microcrystalline Cellulose (b) (4) NF				
Hydroxypropyl Cellulose (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
Microcrystalline Cellulose (b) (4) NF				
Lactose Anhydrous NF				
Crospovidone (b) (4) NF				
Magnesium Stearate NF				
FD&C Blue #2 Aluminum Lake				
(b) (4)				
Naltrexone Hydrochloride (b) (4) USP	8.0			Active ingredient
Microcrystalline Cellulose (b) (4) NF	(b) (4			(b) (4)
Hypromellose USP (b) (4)				
Hydroxypropyl Cellulose (b) (4) NF				
Edetate Disodium USP				
Colloidal Silicon Dioxide NF				
Lactose Monohydrate (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
Opadry II Blue (b) (4)				

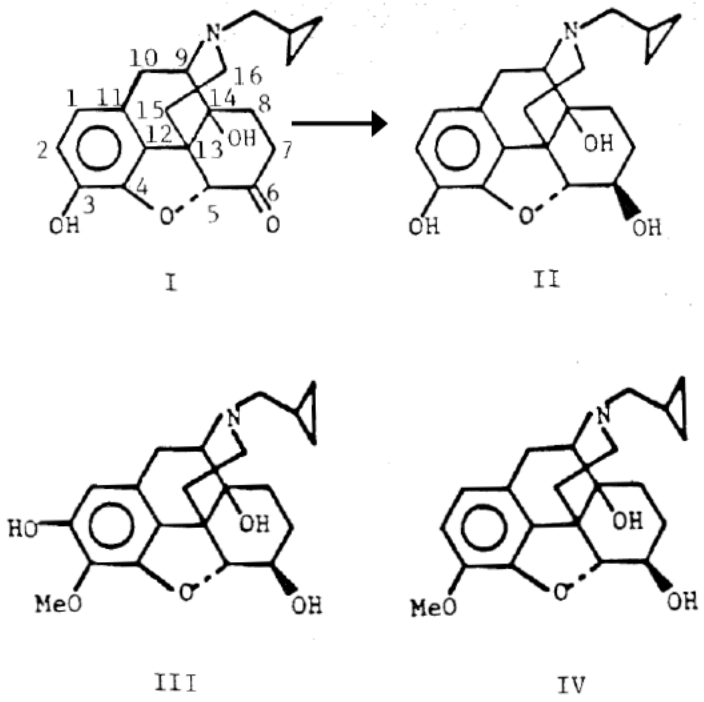
2.2 General Clinical Pharmacology

2.2.1 What are the known genral clinical pharmacology characteristics of naltrexone and bupropion after oral administration, in the context of current application?

The detailed clinical pharmacology information can be found in the prescribing information for the approved naltrexone and bupropion products.

In brief, naltrexone is well-absorbed after oral administration with dose proportional kinetics across IR doses of 50 to 200 mg, but subject to high first pass metabolism limiting oral bioavailability to 5-6%. Naltrexone is metabolized primarily to 6β-naltrexol in humans via cytosolic dihydrodiol-dehydrogenase enzyme system (Figure 8). Both parent and metabolite are subject to conjugation prior to renal excretion. Naltrexone and its metabolic products are primarily excreted in urine. After oral administration, approximately 37-60% of the total dose after oral administration was found to be excreted in urine within 48-72 hr, mainly as conjugated and unconjugated forms of naltrexone and 6β-naltrexol. Multiple once-daily dosing of oral IR naltrexone resulted in no accumulation of parent drug.

Figure 8 **Naltrexone (I), its major metabolite 6β-naltrexol (II), and minor metabolites: 2-hydroxy-3-O-methyl-6β-naltrexol (III), 3-O-methyl-6β-naltrexol (IV)**

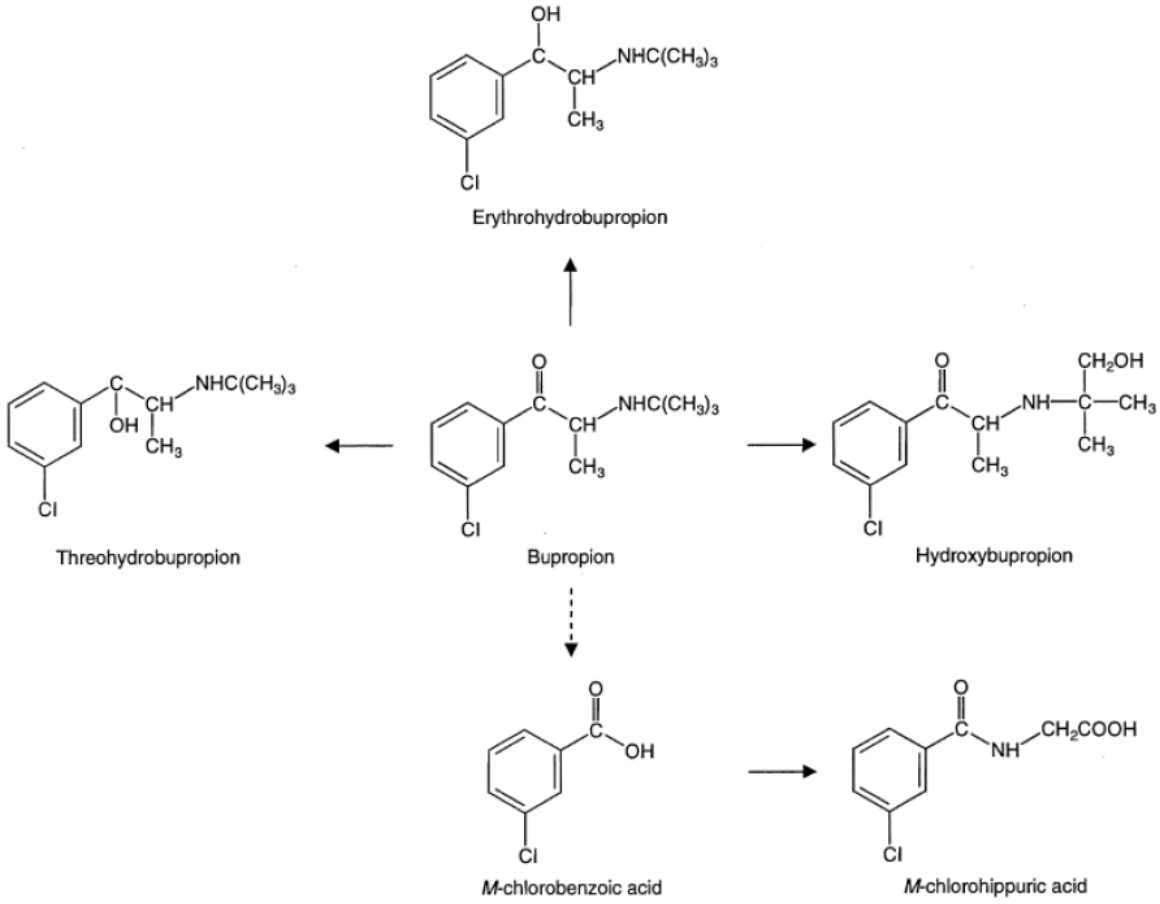


Bupropion is rapidly absorbed after administration of a single 150 mg dose of bupropion SR with a Tmax of approximately 3 hr and a t1/2 of 17-22 hr. The mean elimination t1/2 of bupropion after repeated dosing is 21 hr, and steady-state plasma concentrations of bupropion are reached within 8 days. Oral absorption is expected to be high, as approximately 87% of the administered radioactivity was recovered in urine. Bupropion is extensively metabolized in humans with three key metabolites: 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 (Figure 9).

In vitro findings suggest that cytochrome P4502B6 (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 excreted as the major urinary metabolite.

Bupropion and hydroxybupropion were found to be relatively weak inhibitors of CYP2D6 *in vitro* (IC50 values of 58 µM and 74 µM, respectively). However, a subsequent study reported that erythrohydrobupropion and threohydrobupropion are more potent inhibitors of CYP2D6 than either bupropion or hydroxybupropion, which may explain the larger effect on the PK of CYP2D6 substrates *in vivo* than first predicted from *vitro* data from bupropion and hydroxybupropion alone.

Figure 9 Metabolism of Bupropion



The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, based on 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.

Based on the general belief that bupropion metabolites are active, sponsor of the current application computed a pharmacological weighted composite concentration metric (PAWC) separately for naltrexone and bupropion, weighing in the above mentioned relative potencies for antidepressant activity of the metabolites. Naltrexone PAWC was computed assuming a potency factor of 0.25 for 6 β-naltrexol. PAWC metric was used by the sponsor for PK comparison in Phase 1 clinical pharmacology studies as well as to explain exposure-response for efficacy and safety.

However, there are certain limitations of PAWC metric. The relative potencies of metabolites are based on animal experiments and that relation of anti-depressant activity and weight-loss effect is unknown. The metabolites are referred to as "active" in literature and the product labels but the activity is mentioned without the context or in other words there is no clear answer to the questions "*What are these metabolites active for?"* or *"At what pharmacological receptor these metabolites exert their action, and what is the nature of concentration-response*?". Therefore, any analysis based on the PAWC carry certain assumptions and is exploratory in nature. On the other hand, PAWC metric may represent the worst case scenario from a safety evaluation

perspective as it represents collective measure of exposure to parent and metabolites at a given time.

2.2.2 What are the PK characteristics of naltrexone and bupropion from Contrave formulation after oral administration and how do they relate to the dose?

Single Dose:

The overall trend of mean plasma concentration-time profiles of naltrexone, bupropion, and their metabolites based on pooled Phase 1 PK data from 2 x NB 8/90 mg dose, are illustrated in the Figure 10 below.

The bi-exponential decline was apparent for bupropion and 6β-naltrexol, whereas all other analytes showed a mono-exponential decline. Consistent with the established PK profile for naltrexone and bupropion, the exposure to metabolites is numerically higher than the parent compound for both the drugs.

Figure 10 Mean plasma concentration time profile of naltrexone, bupropion and their metabolites after single oral dose of 2 x NB 8/90 mg under fasted state (pooled Phase 1 data)

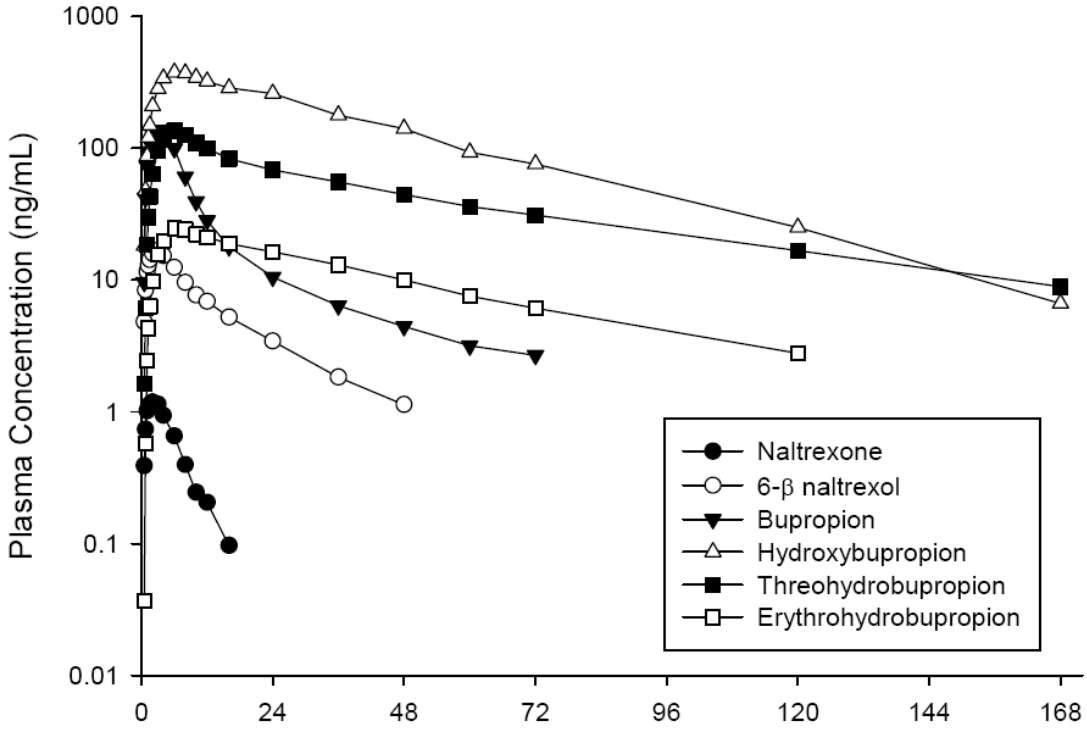


Table 2 Pharmacokinetic parameters of Naltrexone and Bupropion after single oral dose of 2 x 8/90 mg tablet (pooled Phase 1 data) under fasted condition

PK Parameter	Arithmetic Mean ± SD (%CV)[a] [N] Naltrexone	6β-naltrexol
C_{max} (ng/mL)	1.47 ± 1.00 (68.2%) [206]	18.9 ± 6.51 (34.5%) [154]
T_{max} (hr)	2.00 (0.50, 8.00) [206]	3.00 (0.75, 12.00) [154]
$t_{1/2}$ (hr)	4.92 ± 2.35 (47.8%) [198]	13.64 ± 3.43 (25.1%) [153]
AUC_{0-t} (ng·hr/mL)	8.72 ± 5.51 (63.2%) [206]	242.82 ± 65.82 (27.1%) [154]
$AUC_{0-\infty}$ (ng·hr/mL)	9.08 ± 5.62 (61.9%) [198]	261.60 ± 67.22 (25.7%) [153]

	Arithmetic Mean ± SD (%CV)[a] [N]			
	Bupropion	Hydroxybupropion	Threohydrobupropion	Erythrohydrobupropion
C_{max} (ng/mL)	156 ± 49.0 (31.5%) [206]	388 ± 181 (46.6%) [154]	139 ± 54.6 (39.1%) [154]	25.7 ± 7.76 (30.2%) [154]
T_{max} (hr)	3.00 (1.00, 6.11) [206]	6.00 (3.00, 72.00) [154]	6.00 (2.00, 10.00) [154]	6.00 (3.00, 12.00) [154]
$t_{1/2}$ (hr)	21.06 ± 6.31 (30.0%) [204]	26.52 ± 7.02 (26.5%) [152]	46.81 ± 13.47 (28.8%) [146]	31.84 ± 8.64 (27.1%) [149]
AUC_{0-t} (ng·hr/mL)	1415.49 ± 462.28 (32.7%) [206]	16041.06 ± 8768.12 (54.7%) [154]	5531.86 ± 3112.88 (56.3%) [154]	1061.95 ± 429.15 (40.4%) [154]
$AUC_{0-\infty}$ (ng·hr/mL)	1486.63 ± 488.30 (32.9%) [204]	17369.91 ± 9594.63 (55.2%) [152]	6693.09 ± 3665.10 (54.8%) [146]	1240.09 ± 507.81 (41.0%) [149]

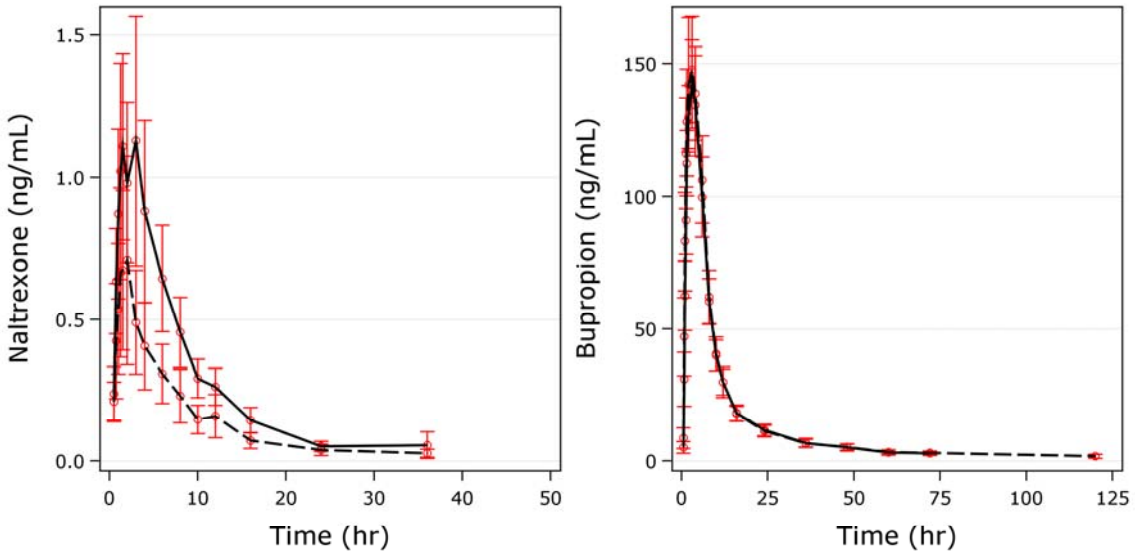
[a] T_{max} is presented as Median (Minimum, Maximum)

Abbreviations: AUC=area under the concentration-time curve from time zero until last quantifiable sample time (0-t) or extrapolated to infinity (0-∞), C_{max}=maximum plasma concentration; N=number of subjects; SD=standard deviation; $t_{½}$=apparent terminal elimination half-life; T_{max}=time to reach maximum plasma concentration; %CV=coefficient of variation.

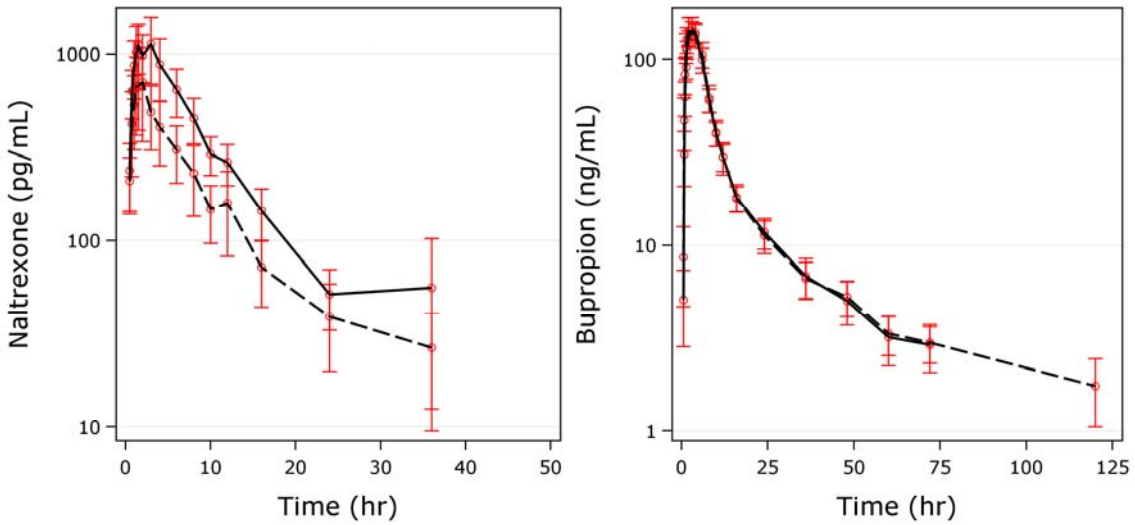
Dose Proportionality:

The two available dose strengths NB 4/90 mg and NB 8/90 mg only differ in terms of (b) (4) The dose proportionality was therefore compared for naltrexone based on dose-normalized PK parameters. Bupropion PK parameters were compared without dose adjustment. The mean plasma concentration-time profiles of naltrexone and bupropion from 2 x NB 4/90 mg and 2 x NB 8/90 mg single doses in Trail NB-232, is illustrated in the Figure 11 below.

Figure 11 Mean(±SE) plasma concentration time profile of naltrexone and bupropion from Contrave formulation after single oral dose of two tablets each of NB 8/90 mg and NB 4/90 mg (Linear and log scale)



(-)2 x NB 8MG/90MG, (--)2 x NB 4MG/90MG
Mean(±)SE Concentration-time Plots by Treatment (Trial NB-232)-Linear Scale



(-)2 x NB 8MG/90MG, (--)2 x NB 4MG/90MG
Mean(±)SE Concentration-time Plots by Treatment (Trial NB-232)-Log Scale
Note: Naltrexone concentrations were converted to pg/mL to plot on Log Scale

The mean concentration time profiles showed dose based increase for naltrexone. As expected, the profiles for bupropion from the two formulations overlapped each other.

The summary statistics of pharmacokinetic parameters for naltrexone and bupropion are presented in Table 3 below.

Table 3 Pharmacokinetic parameters of (a) naltrexone and (b) bupropion after single oral doses of 2 x NB 4/90 mg and 2 x 8/90 mg tablets.

(a): Naltrexone

Naltrexone PK Parameter	Treatment							
	NB 4/90 MG				NB 8/90 MG			
	N	Mean	SD	Median	N	Mean	SD	Median
AUC0-t (ng.hr/mL)	18	4.55	3.94	2.73	18	9.62	5.66	8.64
AUCextrapol (%)	14	5.80	4.04	5.25	16	3.74	2.70	3.10
AUCinf (ng.hr/mL)	14	5.26	4.28	3.45	16	10.55	5.76	9.27
Cmax (ng/mL)	18	0.72	0.65	0.56	18	1.37	0.94	1.14
Tmax (hr)	18	2.60	2.80	1.26	18	2.02	1.21	1.76
t1/2 (hr)	14	4.32	0.93	4.33	16	4.94	1.60	4.64

(b) Bupropion:

Bupropion PK Parameter	Treatment							
	NB 4/90 MG				NB 8/90 MG			
	N	Mean	SD	Median	N	Mean	SD	Median
AUC0-t (ng.hr/mL)	18	1507.24	480.75	1552.70	18	1523.25	500.58	1472.62
AUCextrapol (%)	18	4.40	1.48	4.14	18	5.24	2.07	5.10
AUCinf (ng.hr/mL)	18	1573.06	490.59	1616.91	18	1613.41	549.55	1593.03
Cmax (ng/mL)	18	157.78	41.67	156.50	18	157.19	35.73	153.00
Tmax (hr)	18	2.69	1.10	3.00	18	2.85	0.75	3.00
t1/2 (hr)	18	26.11	7.22	23.19	18	24.74	6.74	22.04

The dose-proportionality assessment, based on statistical analysis of dose-normalized PK parameters of naltrexone and unadjusted PK parameters of bupropion, is presented in Table 4 below. Naltrexone exposure was approximately dose-proportional as the dose-normalized Cmax from NB 4/90 mg formulation was 5% higher and AUCt was 10% lower than those observed from NB 8/90 mg formulation. Bupropion exposure from NB 4/90 mg formulation was bioequivalent to that of the NB 8/90 mg formulation.

Table 4 Dose-proportionality assessment of pharmacokinetic parameters of (a) naltrexone and (b) bupropion after single oral dose

(a) Naltrexone:

PK Parameter [a]	Arithmetic Mean ± SD (%CV)[b] NB 8/90 (Reference)	NB 4/90	%MR (90% CI)[c]
	Naltrexone		
C_{max} (ng/mL/mg)	0.0853 ± 0.0589 (69.1%)	0.0900 ± 0.0812 (90.3%)	105.01 (85.53 - 128.94)
T_{max} (hr)	1.76 (0.75, 6.00)	1.26 (0.97, 12.00)	Not Applicable
$t_{1/2}$ (hr)	4.94 ± 1.61 (32.5%)	4.32 ± 0.93 (21.5%)	Not Applicable
AUC_{0-t} (ng·hr/mL/mg)	0.60 ± 0.35 (58.9%)	0.57 ± 0.49 (86.6%)	89.76 (77.41 - 104.09)
$AUC_{0-\infty}$ (ng·hr/mL/mg)	0.66 ± 0.36 (54.6%)	0.66 ± 0.53 (81.3%)	100.91 (82.67 - 123.19)

(b) Bupropion:

Test	Reference	PK Parameter	Units	Ratio (%)	90% CI
NB 4/90	NB 8/90	AUC(0-inf)	ng.hr/mL	101.57	95.99 - 107.48
		AUC(0-t)	ng.hr/mL	100.93	95.53 - 106.64
		Cmax	ng/mL	102.73	93.72 - 112.59

After single oral dose of Contrave, exposure of metabolites was higher than the parent for both bupropion and naltrexone (Table 5). This shows that 6β-naltrexol and hydroxybupropion are formed as the major circulating metabolites of naltrexone and bupropion, respectively in humans.

Total exposure of threohydrobupropion and erythrohydrobupropion is 5-fold higher and 0.8 fold lower, respectively in comparison to bupropion. This is in line with the information reported in product labels or literature for naltrexone and bupropion. The ratios of metabolite to parent were also consistent for the two formulations.

Table 5 Metabolite to parent ratio after single oral dose in study NB-232

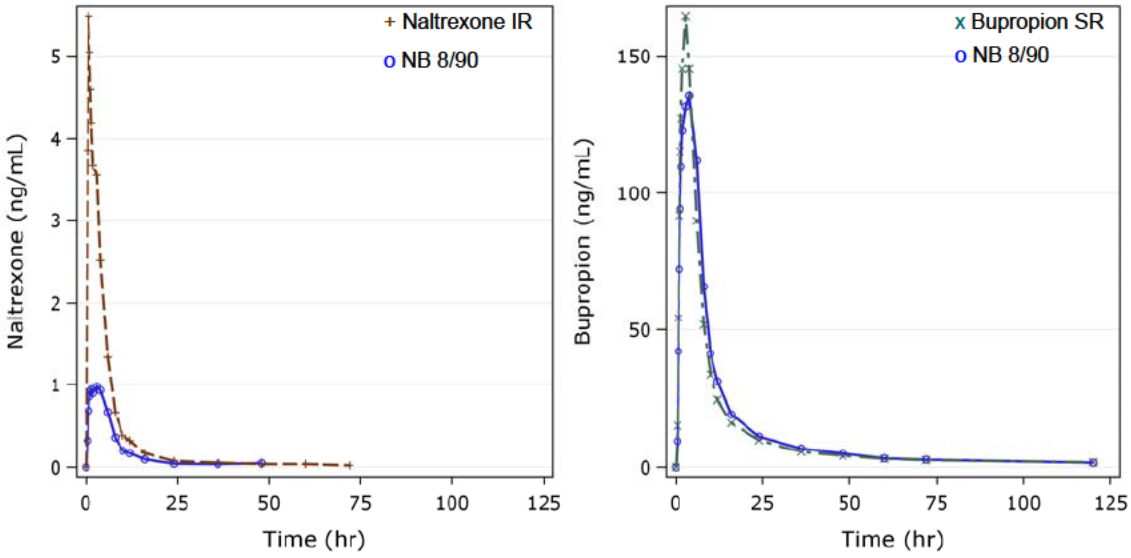
Treatment Description:	2 x NB 4/90 MG			2 x NB 8/90 MG		
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Hydroxybupropion: AUC_{ratio}	17	11.2	5.6	19	12.7	8.4
Hydroxybupropion: $Cmax_{ratio}$	19	2.6	1.6	19	2.5	1.4
Threohydrobupropion: AUC_{ratio}	14	4.0	2.0	16	4.8	2.4
Threohydrobupropion: $Cmax_{ratio}$	19	0.9	0.2	19	0.9	0.3
Erythrohydrobupropion AUC_{ratio}	17	0.8	0.4	19	0.8	0.2
Erythrohydrobupropion: $Cmax_{ratio}$	19	0.20	0.04	19	0.16	0.03
6-Beta naltrexol: AUC_{ratio}	17	28.3	13.2	14	31.5	14.5
6-Beta naltrexol: $Cmax_{ratio}$	19	14.7	6.7	19	15.4	7.8

Single Dose Contrave versus Currently Approved Products:

Mean plasma concentration time profile of naltrexone and bupropion from Contrave formulation (single oral dose of 2 x NB 8/90 mg under fasted state) versus single dose of 50 mg IR formulation and 150 mg Bupropion SR formulation are presented in Figure 12 below.

On average, the exposure of naltrexone from 2 x NB 8/90 mg dose was lower than the 50 mg IR formulation. Whereas, bupropion peak concentrations from 2 x NB 8/90 mg dose appeared to be slightly lower with comparable total exposure to 150 mg bupropion SR formulation.

Figure 12 Mean plasma concentration time profile of naltrexone and bupropion from Contrave formulation (single oral dose of 2 x NB 8/90 mg) versus single dose of 50 mg naltrexone IR and 150 mg Bupropion SR formulation under fasted state



Contrave 2 x NB 8/90 mg, Naltrexone IR 50 mg, Bupropion SR 2 x 150 mg
Mean Concentration-time plots by treatment (Trial NB-230)

Table 6 Summary of pharmacokinetic parameters for naltrexone and bupropion from NB 8/90 mg formulation as compared to commercially available formulations

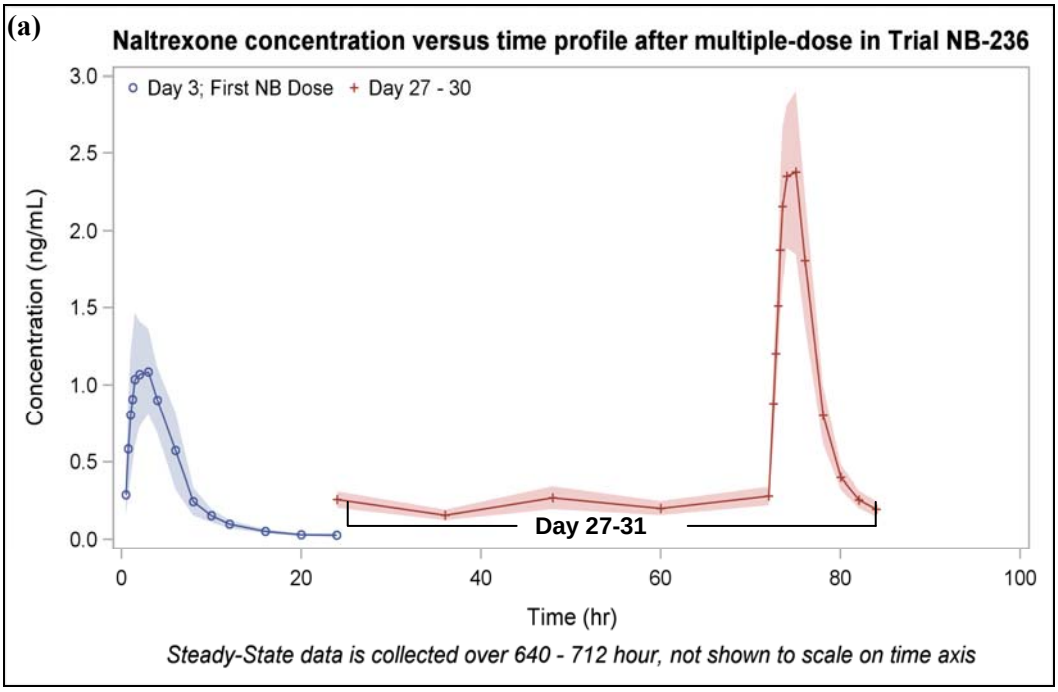
Naltrexone PK Parameters	Treatment							
	2 x NB 8/90 mg				Naltrexone 50 mg IR			
	N	Mean	SD	Median	N	Mean	SD	Median
AUC0-t (ng.hr/mL)	27	7.81	4.53	6.54	26	24.78	12.59	19.55
AUCextrapol (%)	26	4.23	3.41	3.55	24	1.61	0.95	1.37
AUCinf (ng.hr/mL)	26	8.17	4.63	7.07	24	25.92	12.87	20.24
Cmax (ng/mL)	27	1.33	0.91	0.99	26	7.24	4.58	5.69
t1/2 (hr)	26	5.22	2.29	4.90	24	7.05	2.70	6.63
Tmax (hr)	27	2.27	1.37	2.00	26	1.17	0.75	1.00

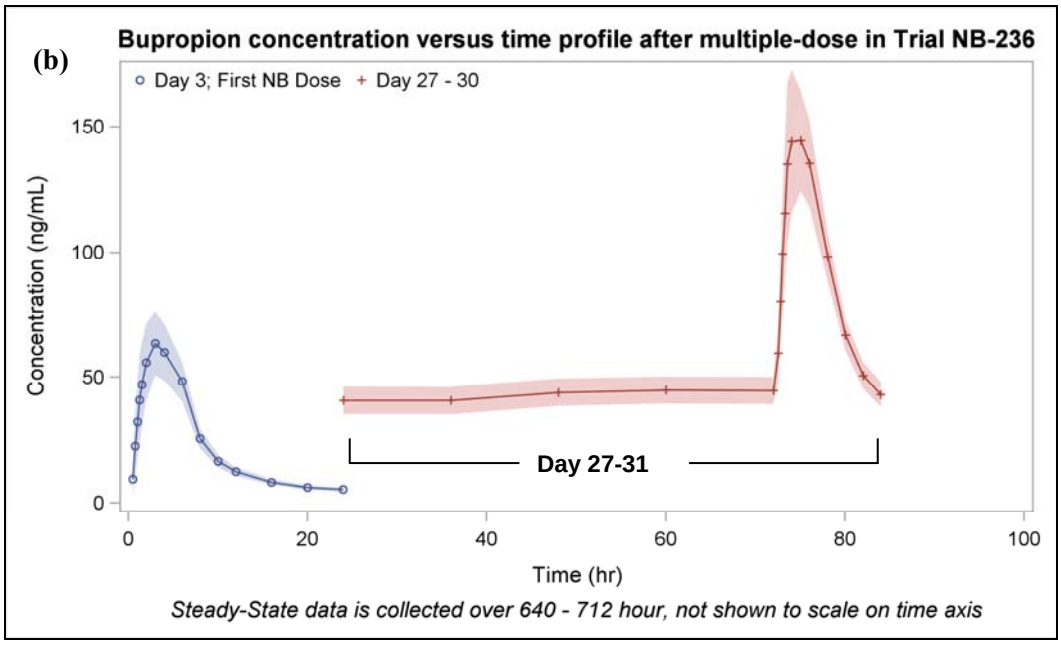
Bupropion PK Parameters	Treatment							
	2 x NB 8/90 mg				Bupropion 150 mg SR			
	N	Mean	SD	Median	N	Mean	SD	Median
AUC0-t (ng.hr/mL)	27	1511.84	409.74	1434.82	26	1427.15	386.75	1400.66
AUCextrapol (%)	27	4.10	1.95	3.67	26	4.32	1.92	4.07
AUCinf (ng.hr/mL)	27	1573.93	421.84	1473.65	26	1492.20	406.06	1434.02
Cmax (ng/mL)	27	165.79	53.66	158.00	26	172.25	57.87	161.50
t1/2 (hr)	27	21.38	5.71	19.91	26	22.23	7.08	21.09
Tmax (hr)	27	3.32	1.47	3.00	26	2.89	0.81	3.00

Multiple Doses:

Multiple dose PK was assessed for naltrexone and bupropion in the DDI study with metoprolol. Following Day 1 single (morning) dose of a metoprolol 50 mg IR tablet and a 2-day washout period (fed), once daily (morning) doses of 1 x NB 8/90 mg were administered on days 3 to 9 (fed). Days 10 to 16 twice daily (morning and evening) doses of 1 x NB 8/90 mg (fed). On days 17 to 23 morning doses of 2 x NB 8/90 mg tablets and evening doses of 1 x NB 8/90 mg (fed) were administered. On days 24 to 30 twice daily (morning and evening) doses of 2 x NB 8/90 mg tablets (fed) were administered. PK data for bupropion was collected on Day 3 and Day 27 on wards. The mean (95%CI bands) plasma concentration-time profile of NB after single oral dose (on Day 3) and multiple twice daily oral doses (Day 27-30) is summarized in Figure 13a and 13b, respectively for naltrexone and bupropion.

Figure 13 Mean (95%CI bands) Plasma concentration-time profile of naltrexone (a) and (b) bupropion after single oral dose of 1 x NB 8/90 mg (on Day 3) and after multiple twice daily oral doses of 2 x NB 8/90 mg (steady state assessed on Day 27-30)





Following multiple daily dosing according to the titration scheme explained above, naltrexone and bupropion apparently achieved steady-state for the 2 x NB 8/90 mg BID dosing as evident from Day 27-30 trough concentration time profile. Bupropion showed accumulation after multiple doses as was expected based on ~24 hr t1/2 and 12 hr dosing interval. Whereas, accumulation was not evident for the naltrexone component, (calculated dose-adjusted accumulation ratio of 7%), which is consistent with the shorter t1/2 of 4 hours and 12 hr dosing interval. Unlike naltrexone, approximately 2-fold dose-adjusted accumulation of 6β-naltrexol was expected for twice daily dosing given its t½ of approximately 13 hr, but the observed accumulation ratio of approximately 3-fold was higher than expected value.

Metabolite-to-parent ratios after single oral dose of 1 x NB 8/90 mg and at steady state are presented in Table 6 and 7, respectively. After single oral dose of 1 x NB 8/90 mg, for 6β-naltrexol, the AUC value was approximately 30-fold greater and the Cmax value was approximately 15-fold greater than for parent drug. AUC for hydroxybupropion and threohydrobupropion after single dose were 12- and 4-fold higher, respectively, than bupropion values, but only a slightly higher AUC was observed for erythrohydrobupropion relative to parent drug.

At steady-state 6β-naltrexol AUC value was approximately 45-fold greater and the Cmax value was approximately 25-fold greater than for parent drug. Exposure parameters for hydroxybupropion and threohydrobupropion at steady state were substantially higher than bupropion values, but only a slightly higher AUC was observed for erythrohydrobupropion relative to parent drug. Thus both parent components and their metabolites accumulated at steady-state.

Table 7 Metabolite to parent ratio after single oral dose on Day 3 in study NB-236

Treatment Description:		1 x NB 8/90 mg		
Variable		**N**	**Mean**	**SD**
Hydroxybupropion:	AUC_{ratio}	36	11.9	7.0
Hydroxybupropion:	$Cmax_{ratio}$	38	2.6	1.5
Threohydrobupropion:	AUC_{ratio}	30	4.4	2.2
Threohydrobupropion:	$Cmax_{ratio}$	38	0.9	0.3
Erythrohydrobupropion	AUC_{ratio}	36	0.8	0.3
Erythrohydrobupropion:	$Cmax_{ratio}$	38	0.16	0.04
6-Beta naltrexol:	AUC_{ratio}	31	30.0	13.8
6-Beta naltrexol:	$Cmax_{ratio}$	38	15.0	7.2

Table 8 Mean (±SD) metabolite to parent ratios for naltrexone and bupropion metabolites after multiple twice daily oral doses (Day 27-30)

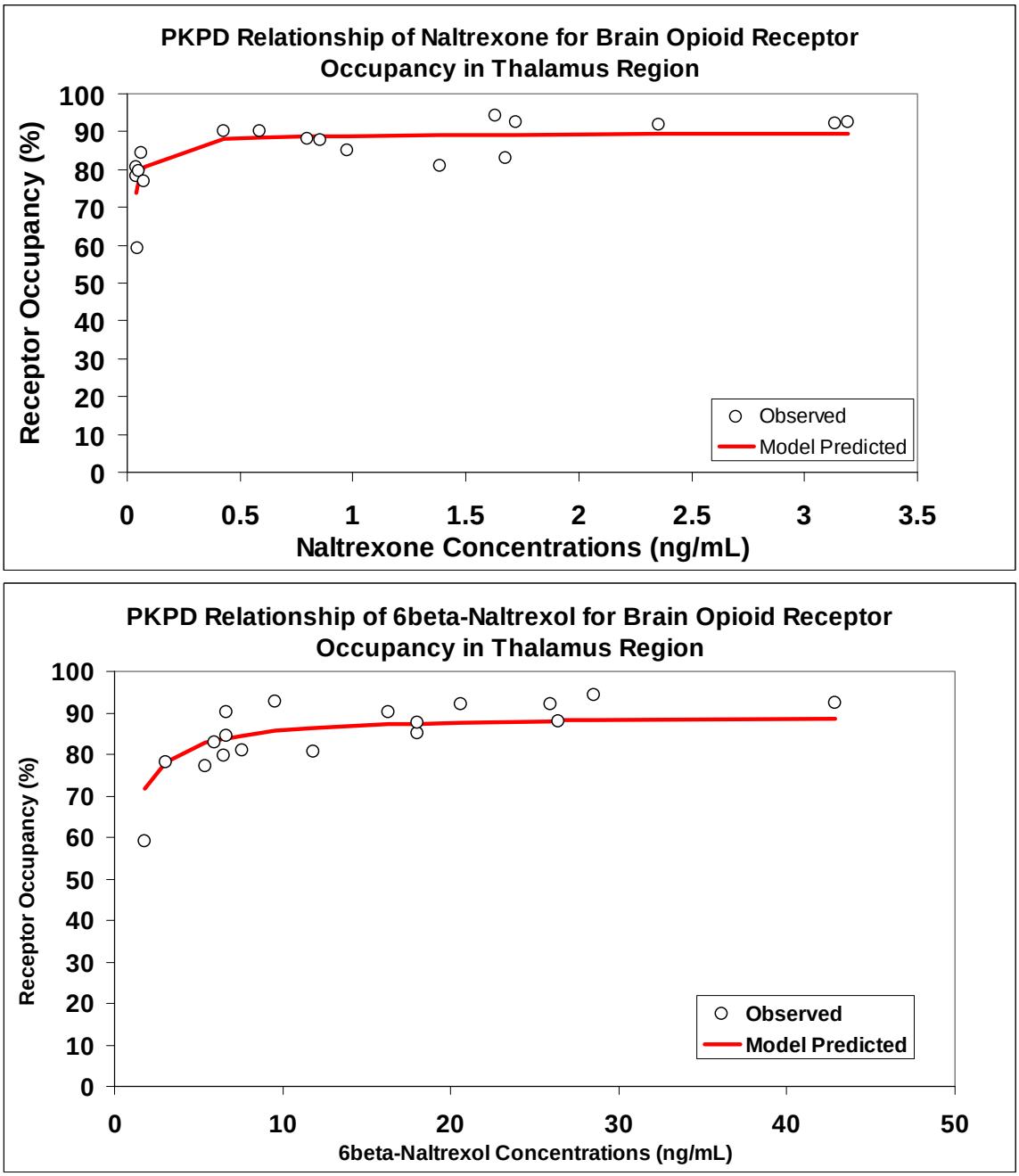
Plasma 6β-naltrexol	
$AUC_{ratio\ M\text{-}P}$	44.56 ± 20.91
$Cmax_{ratio\ M\text{-}P}$	24.47 ± 10.15
Plasma Hydroxybupropion	
$AUC_{ratio\ M\text{-}P}$	16.75 ± 5.75
$Cmax_{ratio\ M\text{-}P}$	11.00 ± 4.24
Plasma Threohydrobupropion	
$AUC_{ratio\ M\text{-}P}$	7.39 ± 1.76
$Cmax_{ratio\ M\text{-}P}$	4.92 ± 1.41
Plasma Erythrohydrobupropion	
$AUC_{ratio\ M\text{-}P}$	1.53 ± 0.38
$Cmax_{ratio\ M\text{-}P}$	0.99 ± 0.29

2.2.3 What are the pharmacodynamic characteristics of NB after oral administration and how do they relate to the dose?

As mentioned earlier, based on proposed mechanism of action, naltrexone/bupropion in combination possibly act as a dual POMC enhancer by stimulating activity of POMC and simultaneously antagonizing mu-opioid receptors on these same cells. Naltrexone is believed to block opioid receptors on POMC cells, and thus could amplify the effect of bupropion.

To optimize the dose for naltrexone, Sponsor conducted a clinical pharmacology study to determine the CNS opioids receptor occupancy by controlled-release naltrexone. This study showed that % occupancy of opioids receptor exceeded 80% at concentration as low as 0.1 ng/mL (Figure 14).

Figure 14 **PKPD Relationship of naltrexone and 6-beta naltrexol for brain opiate receptor occupancy**



The results of another study IR-PET showed that naltrexone twice daily dosing for 7 days resulted in average receptor occupancy in excess of 80% for the 24 mg dose. For the 16 mg dose, receptor occupancy remained above 80% for approximately 6 hours. Average receptor occupancy for the 8 mg naltrexone dose was greater than 70% for at least 6 hours. At 16 and 24 mg naltrexone twice daily, the receptor occupancy remained above 60% for up to 24 hours. The study results support the selection of total maximum daily dose of naltrexone component in Contrave (32 mg). However, the relevance of 60% lower cut-off used by the sponsor for the opioid receptor occupancy is not well understood.

Table 9 Dose-Response for brain opioids receptor occupancy in study IR-PET

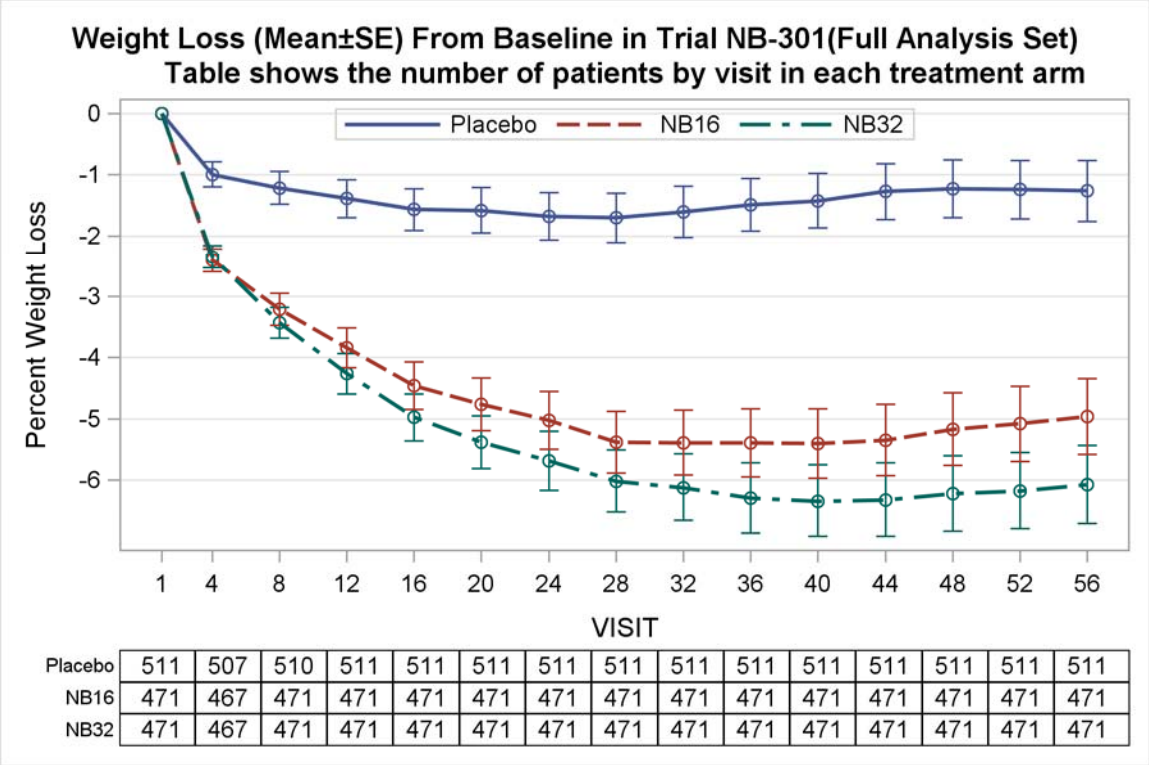
Dose	Time	Mean	SD	90% CI Lower	90% CI Upper
8	1	74.63	4.03	72.13	77.13
8	6	70.70	4.34	68.01	73.39
8	24	53.50	5.74	49.94	57.06
16	1	88.37	4.30	85.71	91.03
16	6	76.70	4.11	74.16	79.25
16	24	64.37	4.88	61.34	67.40
24	1	87.59	3.68	85.31	89.88
24	6	84.96	4.34	82.27	87.65
24	24	74.19	5.43	70.82	77.55

Abbreviations: CI=confidence interval; SD=standard deviation; IR=immediate release.
Note: doses were administered twice daily.

2.2.4 What are the characteristics of the exposure-response relationship (dose-response, concentration-response) for weight loss in obese patients?

The percent weight loss versus time profile from Phase 3 trial NB-301, which tested two doses (NB 16/360 and NB 32/360) is presented in Figure 15 below. The trial results show that the maximal mean percent reduction in weight from baseline is achieved after week 28 in both low (NB 16/360) and high dose (NB 32/360) treatment arms. These two treatment arms differed in the total daily naltrexone dose; 16 mg versus 32 mg, while receiving same total daily dose of 360 mg Bupropion.

Figure 15 Time course of percent weight loss from baseline in the 56-week Phase 3 confirmatory trial (NB-301)



The dose-weight loss relationship at week 56 from this trial shows that Contrave treatment is associated with a dose dependent reduction in weight from baseline (Figure 16). However, the weight loss with Contrave treatment was marginal as the maximal placebo adjusted weight loss was 4.8%, achieved with the NB 32/360 mg dose. This efficacy result does not satisfy one of the two efficacy benchmarks recommended in the FDA Guidance document on "Developing Products for Weight Management".

According to the Guidance "*In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:*

• *The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*

• *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant"*.

NB 32/360 mg dose also shows a numerical advantage over NB 16/360 mg dose with regards to maximal weight loss (See Table 10 below).

Figure 16 Dose dependent increase in effectiveness of Contrave based on Mean (±SE) % Weight Loss from baseline at week 56 (Phase 3 trial NB-301)

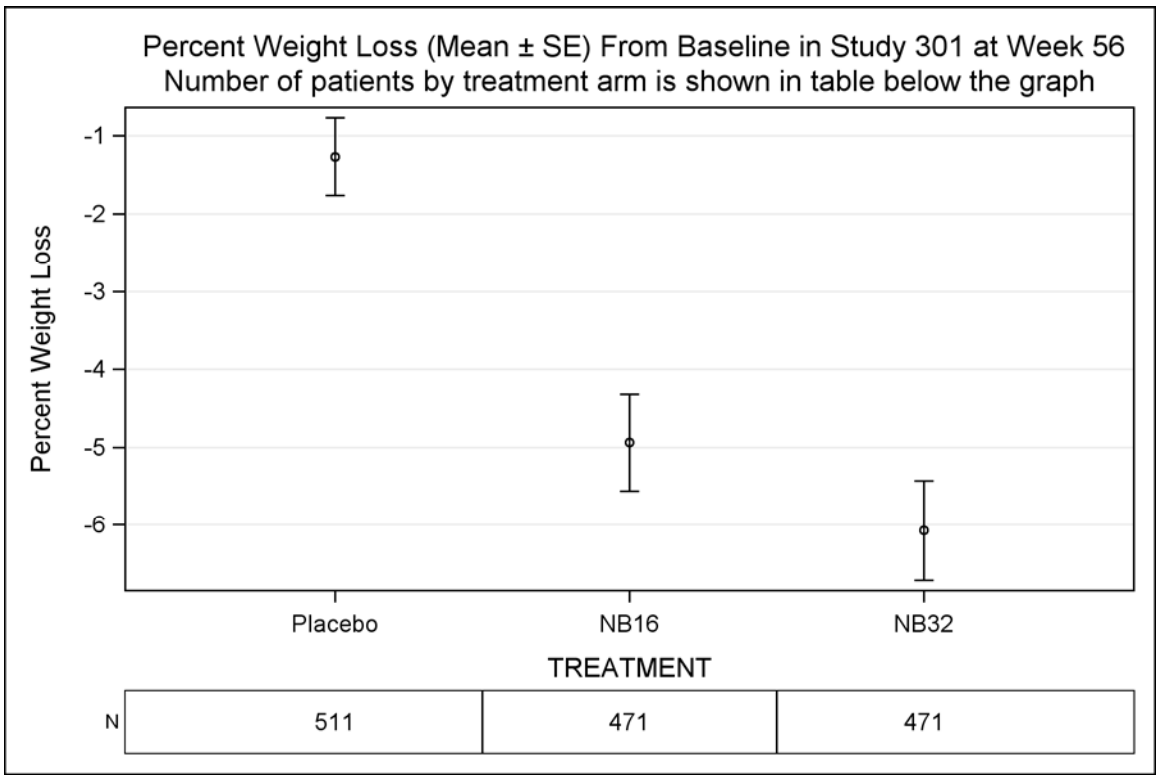


Table 10 Body Weight (kg), Percent Change from Baseline to Endpoint in Trial NB-301 (Full Analysis Set)

Statistic	Placebo (n=511)	NB16 (n=471)	NB32 (n=471)
Baseline mean (SD)	99.29 (14.33)	100.11 (14.41)	100.17 (16.26)
% change from baseline, LSMean (SE)	-1.33 (0.30)	-5.00 (0.31)	-6.14 (0.31)
LSMean difference from placebo (SE)	--	-3.67 (0.42)	-4.81 (0.42)
95% CI	--	(-4.50, -2.85)	(-5.63, -3.99)
p-value	--	< 0.001	< 0.001
LSMean difference from NB16	--	--	-1.14
95% CI	--	--	(-1.98, -0.30)
p-value	--	--	0.008

Abbreviations: NB16=Naltrexone SR 16 mg/Bupropion SR 360 mg, NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg, CI=Confidence Interval
(**Reference: Table 2.7.3-2 Section 2.7.3 Summary of Clinical Efficacy Page 13)**

Numerical benefit of NB 32/360 mg dose was also evident from a greater percentage of subjects loosing >5% weight with this dose against NB16/360 mg and placebo (see Table 11 below). Thus, this efficacy result met second efficacy benchmark recommended by the Guidance.

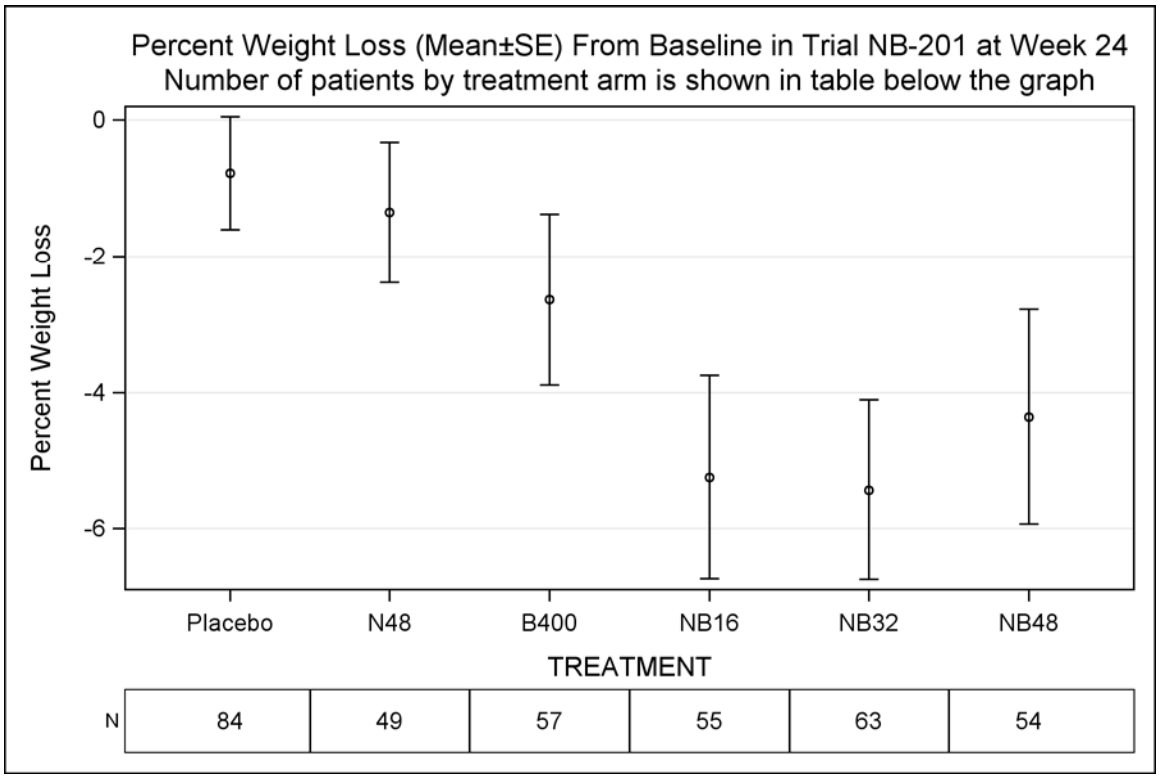
Table 11 Proportion of patients achieving ≥5% Weight Loss at Endpoint by Treatment in Trial NB-301 (Full Analysis Set)

Statistic	Placebo (n=511)	NB16 (n=471)	NB32 (n=471)
No. (%) with ≥ 5% decrease	84 (16.44%)	186 (39.49%)	226 (47.98%)
95% CI	(13.22%, 19.65%)	(35.08%, 43.91%)	(43.47%, 52.49%)
Odds ratio vs. placebo	--	3.42	4.86
95% confidence limit for odds ratio	--	(2.52, 4.63)	(3.60, 6.57)
p-value	--	< 0.001	< 0.001
Odds ratio vs. NB16	--	--	1.42
95% confidence limit for odds ratio	--	--	(1.09, 1.85)
p-value	--	--	0.010

Abbreviations: NB16=Naltrexone SR 16 mg/Bupropion SR 360 mg, NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg, CI=Confidence Interval
(**Reference: Table 2.7.3-3 Section 2.7.3 Summary of Clinical Efficacy Page 14)**

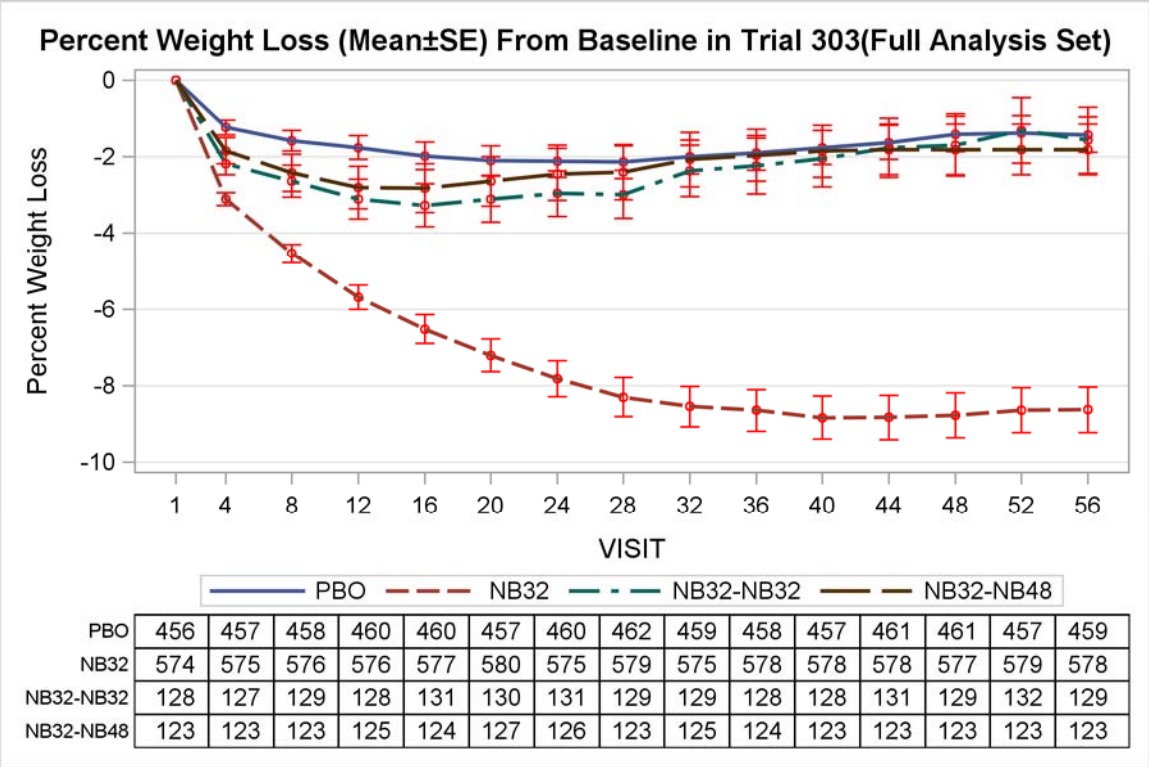
Dose-response data from Phase 2 trial also demonstrated that co-administration of Naltrexone (16 or 32 mg total daily dose) and Bupropion (400 mg total daily dose) results in additive increase in weight loss over the monotherapy with Naltrexone (48 mg total daily dose) or Bupropion (400 mg total daily dose). However, the NB48 treatment did not show any benefit over the NB16 or NB32 treatments and the B400 (Bupropion 400 mg monotherapy treatment (see Figure 17 below).

Figure 17 Combination of Naltrexone and Bupropion results in additive weight loss versus monotherapy based on Mean(±SE) % Weight Loss from baseline at week 24 (Phase 2 trial NB-201)



Phase 3 Trial NB-303 also tested the dose escalation to NB48 (Naltrexone 48 mg and Bupropion 360 mg total daily dose) for subjects who did not loose >5% weight by Week 28. The percent weight loss versus time by treatment arms in Trial NB-303 is presented in Figure 18 below. The escalation of dose to NB48 did not show any benefit with regards to improvement in weight loss among non-responders to their baseline treatment.

Figure 18 **Time course of percent weight loss from baseline by pooled treatment arms in the 56-week Phase 3 confirmatory trial (NB-303).**



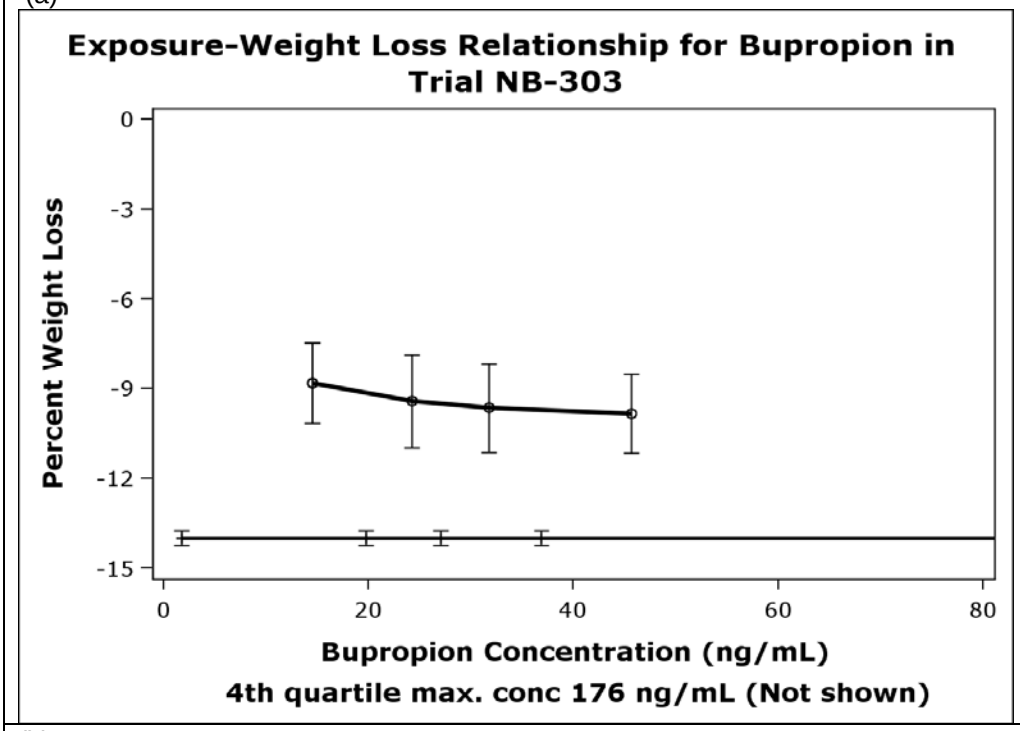
PBO	456	457	458	460	460	457	460	462	459	458	457	461	461	457	459
NB32	574	575	576	576	577	580	575	579	575	578	578	578	577	579	578
NB32-NB32	128	127	129	128	131	130	131	129	129	128	128	131	129	132	129
NB32-NB48	123	123	123	125	124	127	126	123	125	124	123	123	123	123	123

PBO: Placebo subjects, NB32: Subjects on active treatment who lost 5% or greater weight by week 28, **NB32-NB32:** Subjects loosing less than 5% weight and re-randomized to receive NB32, **NB32-NB48:** Subjects loosing less than 5% weight and re-randomized to receive NB48.

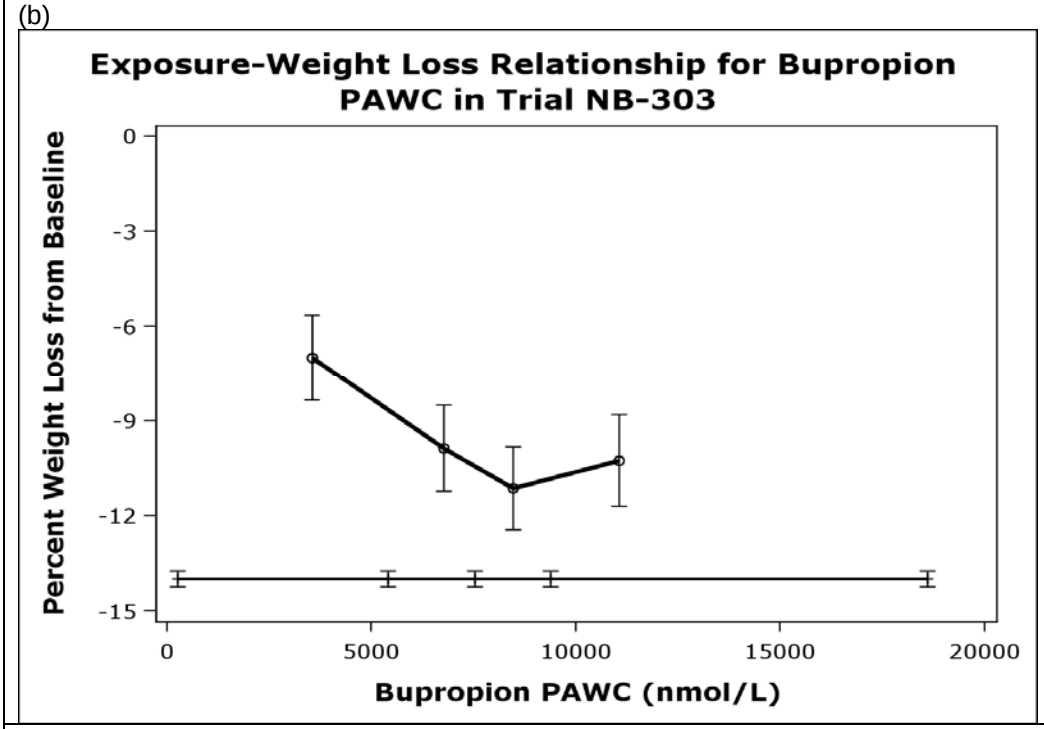
With regards to the concentration-response, there was a shallow trend of increase in weight loss with increase in bupropion exposure. Similar trend was observed with increasing bupropion PAWC, naltrexone PAWC in the exploratory analysis using these metric. For FDA's exploratory exposure-response PAWC was computed as sum of parent and metabolite concentrations in nM, without applying the potency factors for metabolites. Percent weight loss (Mean±SE) was plotted against the median of each of the four quartiles for bupropion PAWC concentration (see Figure 19)

Figure 19 Systemic exposure-response from the 56-week Phase 3 trial (NB-303)

(a)



(b)



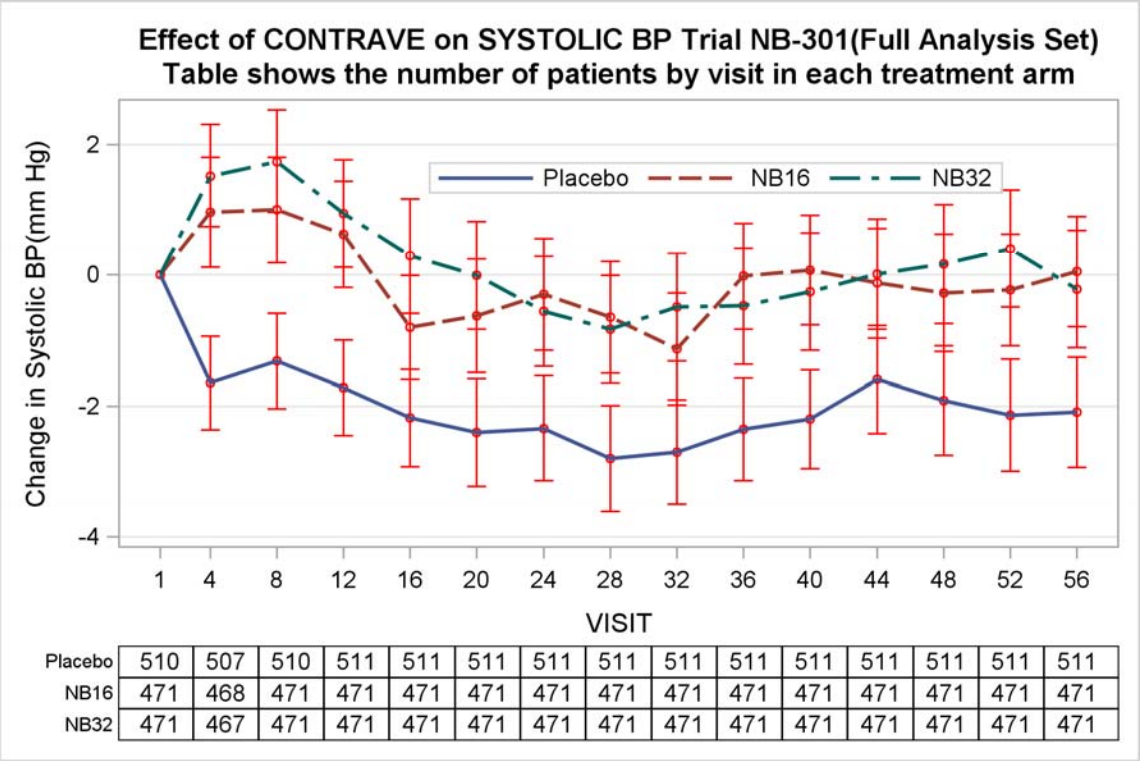
Note: FDA computed naltrexone or bupropion PAWC as sum of parent and metabolite concentrations in nM, without applying the potency factors for metabolite(s)

2.2.5 What are the characteristics of the exposure-response relationship (dose-response, concentration-response) for blood pressure effects and with regards to gastro-intestinal and psychiatric adverse reactions in obese patients?

Effects of Contrave Treatment on Blood Pressure:

Effect on Blood Pressure: Bupropion is known to increase the blood pressure through unknown mechanism. Contrave treatment was also associated with an increase in systolic blood pressure (SBP) in obese patients. Data from placebo controlled Trial NB-301, which tested two dose levels of the combination (bupropion dose was same 360 mg/day), showed that the maximum mean increase of around 1 to 2 mm Hg from baseline was observed up to Visit 8 with the active treatment arms. This mean rise in systolic BP returned to baseline by week 16. The placebo group showed greater reduction in BP from baseline.

Figure 20 Mean (SE) systolic blood pressure change from baseline in the 56-week Phase 3 confirmatory trial (NB-301).



Other three Phase 3 trials used one dose of bupropion (360 mg/day). Therefore, longitudinal blood pressure and pulse rate data collected in the Phase 3 trials was pooled and evaluated by treatment arms, against placebo. Pooled data from placebo controlled trials NB-301, NB-302, NB-303 and NB-304 showed that the responders in placebo and active treatment group have greater reduction in BP from baseline when compared to the non-responders. Similar trends were observed for Diastolic Blood Pressure and Pulse Rate (see Pharmacometric Review in Appendix 4.2). Therefore, overall the beneficial effect of weight loss in terms of reduction in BP was absent in the Contrave treatment group.

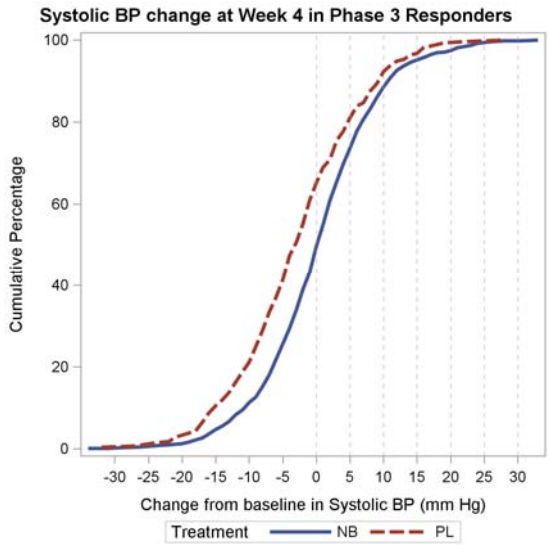
To determine the risk to patients with respect to the maximum BP increase, cumulative percentage of subjects were plotted versus the change in BP for the pooled Phase 3 data for active (NB32) versus the placebo treatments, both at week 4 and 56, stratifying by responder/non-responder status (subjects who lost 5% or more weight from baseline at week 56). The plots

clearly showed a distinction between the placebo and active treatment arms regardless of the response group (shift to the right) (Figure 21).

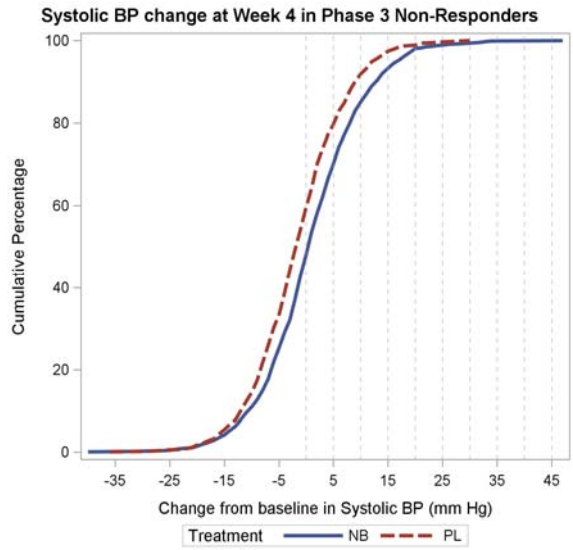
Based on the cumulative frequency distribution top 5% of responder patients in the Contrave treatment arm had ~2 mm Hg increase from baseline over the top 5% placebo responders at Week 4. At week 56, this difference was ~3 mm Hg in top 5% patients among responders. Among the non-responder population, this difference against placebo was ~5 and 3 mm Hg at Week 4 and 56, respectively.

Figure 21 Cumulative Percentage of Subjects versus Systolic BP Change from Baseline by Treatment in Pooled Data from Phase 3 confirmatory trials

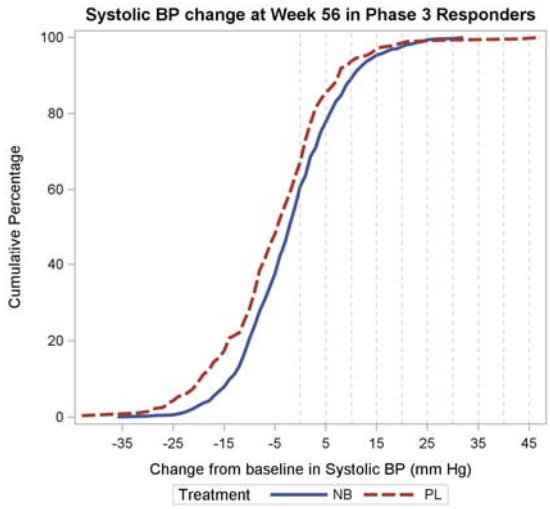
(a) Week 4–Responder



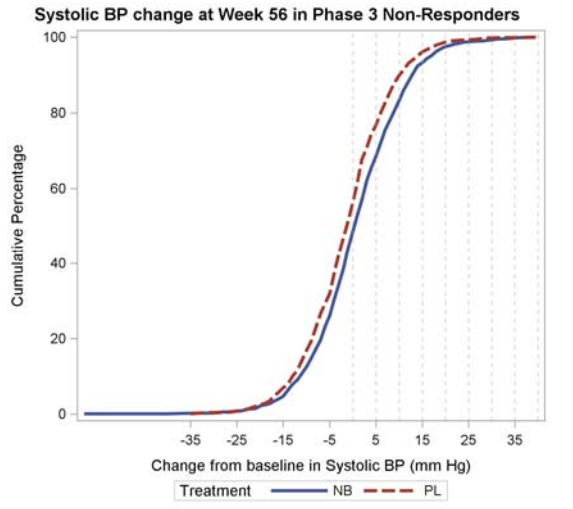
(b) Week 4 – Non Responders



(c) Week 56 – Responders



(d) Week 56 – Non-Responders

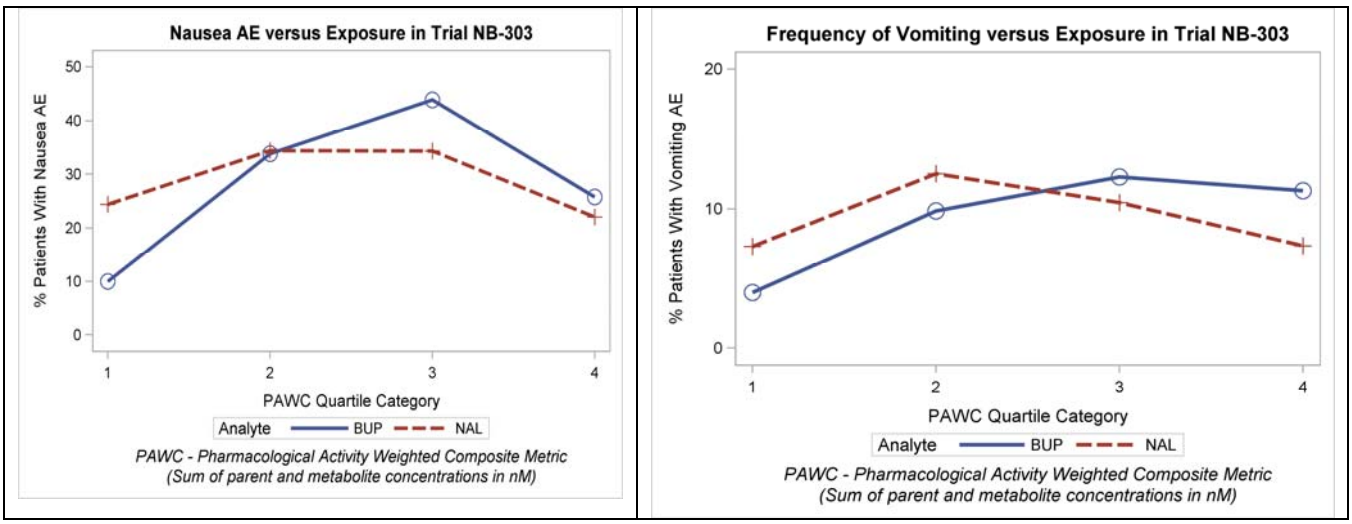


Mean change in Systolic BP from baseline in Trial NB-303, however, did not show any trend with increasing bupropion exposure based on the exposure-response analysis. This is more likely due to the fact that PK subset happen to be the patients who lost more weight than those in whom PK data was not collected (see Pharmacometric Review for details).

Treatment Emergent Gastro-intestinal and Psychiatric Adverse Events (TEAEs):

Systemic exposure-response analysis for GI and Psychiatric TEAEs from Phase 3 trial Nb-303 showed that the percentage of subjects with vomiting and to some extent nausea increased with increase in the bupropion PAWC metric (Fig. 18) across four PAWC quartiles. No such relationship was apparent with increase in naltrexone PAWC metric across four quartiles. Percentage of subjects with insomnia and anxiety did not show increase with bupropion, bupropion PAWC, naltrexone or naltrexone PAWC metrics.

Figure 22 Exposure-Response for Treatment Emergent Adverse Events of Nausea and Vomiting in 56-week Phase 3 confirmatory trial (NB-303)

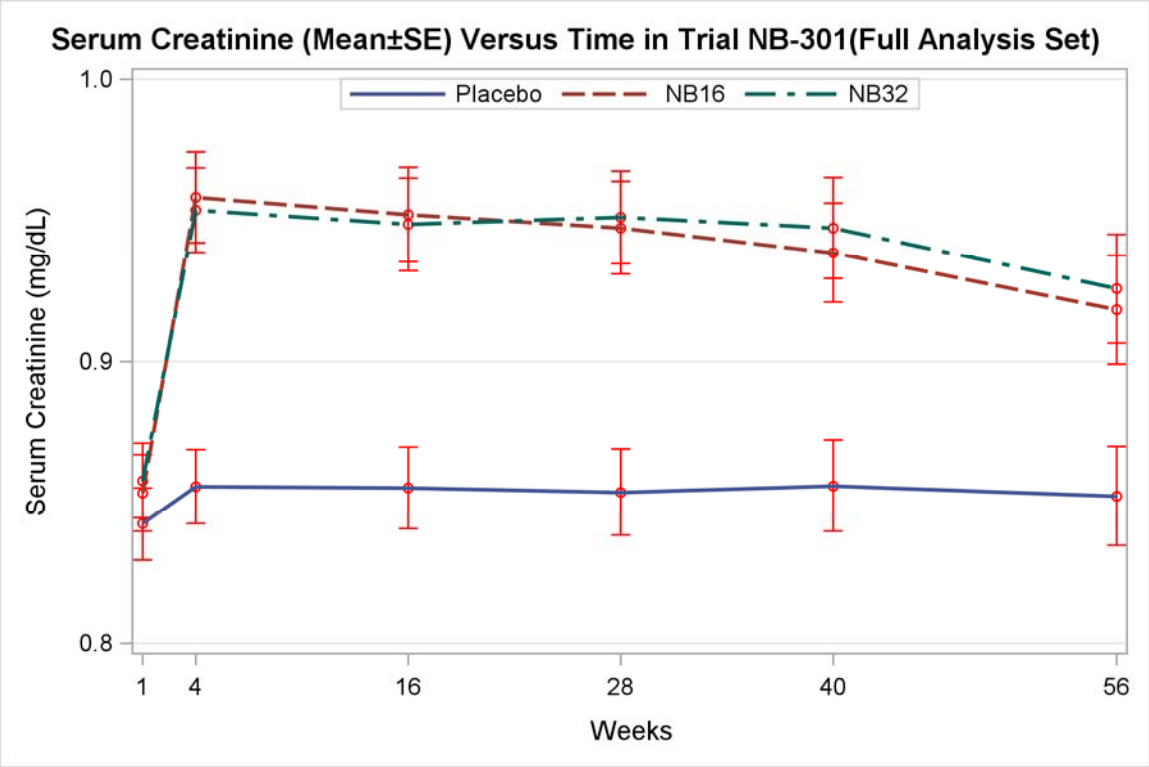


Effects on Serum Creatinine:

The clinical trial data showed increase in serum creatinine from baseline in the Contrave treated patients. A representative graph from one of the Phase 3 trial NB-301 is shown in Figure 23 below.

To explain the plausible mechanism, sponsor provided an in vitro DDI study report. This in vitro study was conducted to evaluate the ability of bupropion and its metabolites or naltrexone and its metabolite in inhibiting organic cation transporter (OCT2) in the kidney. OCT2 is involved in tubular secretion of creatinine and other drugs e.g. metformin. The in vitro study results demonstrated that bupropion and its metabolites, specifically threohydrobupropion and erythrohydrobupropion inhibit Organic Cation Transporter (OCT2) with Cmax, free/IC50=0.29 (Ratio>0.1 is considered clinically relevant). Thus, slight increase in serum creatinine noted in the Phase 3 trials could be due to OCT2 inhibition.

Figure 23 Serum creatinine versus time by treatment in Trial NB-301



2.2.6 Does this drug prolong the QT or QTc Interval?

A formal consult to review the QTc data was submitted to the IRT. Based on the IRT review the following observations were made:

According the IRT Review, large changes in QTc intervals were not observed in studies NB-228 and NB-303. However, the trial design is not sufficient to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms), as defined by ICH E14 guidance. The review noted following limitations:

- No positive control was included in Study NB-228 or Study NB-303 to demonstrate assay sensitivity.
- In both studies the number of ECGs collected was insufficient to capture the potential maximum QTc prolongation.
- In Study NB 303, PK samples were collected incorrectly. For some subjects, there is no time-matched PK sampling. For other subjects, PK was collected immediately prior to ECG assessment.
- It is unclear whether adequate number of subjects was included in the trial to rule out small changes in QTc interval, as defined by ICH E 14 guidance.

2.3 Intrinsic Factors

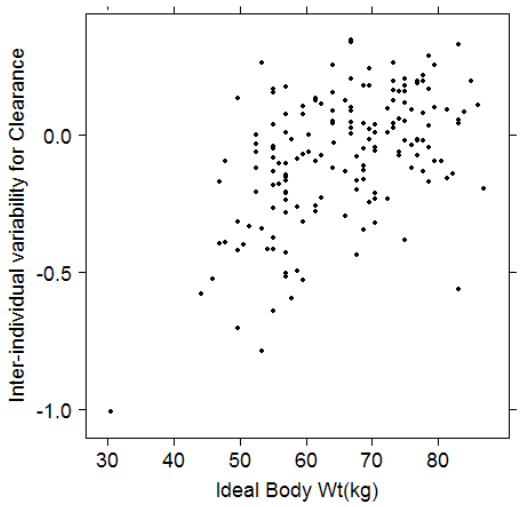
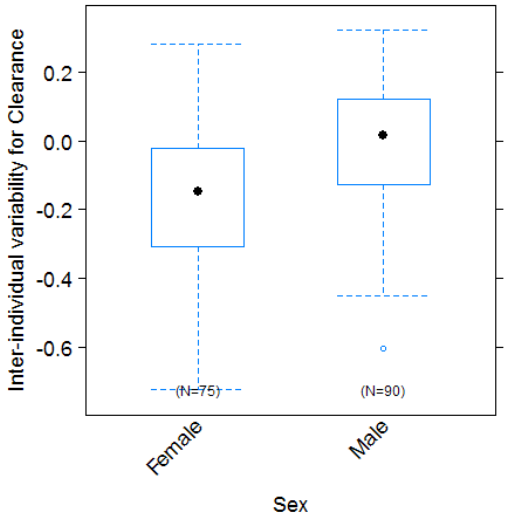
2.3.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or

response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of various covariates e.g. Ideal body weight, Weight, Age, BMI, Gender and Race was assessed in the population pharmacokinetic analysis. The details are mentioned in the Pharmacometric review under Appendix 4.2. Highlights of the results for bupropion and naltrexone are described below:

Bupropion: Ideal body weight was found to influence the apparent clearance of bupropion, as shown in Figure 24a. However, the relationship between ideal body weight and clearance was shallow (Exponent 0.43) and it only explained 5% points of inter-indiviual variability (IIV) in CL/F. The apparent volume of distribution Vc/F increased with increasing ideal body weight (Exponent 1.12), and ideal body weight explained 10% points of IIV in Vc/F.

Figure 24 Bupropion clearance increases with increase in ideal body weight

(a) Inter-individual variability in bupropion clearance versus Ideal Body Weight from base model	(a) IBW adjusted Clearance versus Gender
	

According to the sponsor's analysis, bupropion F was higher in women when compared with men, with an estimate of 1.20 (1.08, 1.37) relative to men. There was an almost 50% probability of bupropion bioavailability for females being greater than 125% of the typical male, suggesting that sex may have an influence on bupropion first-pass metabolism. The ideal body weight adjusted clearance on average showed difference among males and females (Figure 24b).

The effect of age or race (Whites versus Non-whites) on bupropion clearance was not evident from the data.

2.3.2 Does the renal function affect NB pharmacokinetics?

Naltrexone, 6β-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion and their conjugates are excreted in urine. Renal clearance of 6β-naltrexol also involves active tubular secretion. Adequate studies of naltrexone in patients with

severe renal impairment have not been conducted. Based on the bupropion product labels, there is limited information on the pharmacokinetics of bupropion in patients with renal impairment.

The available limited data suggests that the elimination of bupropion and/or the major metabolites of bupropion is reduced by impaired renal function. Exposures in patients with end stage renal failure could be as high as 2.3- and 2.8-fold for hydroxybupropion and threohydrobupropion metabolites. While another 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 threohydro/erythrohydrobupropion (combined) metabolites were similar in the 2 groups.

Contrave clinical program included mild and moderate renal impairment subjects for which PK data was available in Trial NB-303. The data from this trial was used for population PK analysis in obese subjects. There were 4 subjects with creatinine clearance values 30-59 mL/min (moderate) and 69 subjects with creatinine clearance values between 60-90 mL/min (mild impairment). Population PK analysis of data from NB-303 trial revealed that apparent bupropion and naltrexone clearance was not influenced by creatinine clearance over the range of 53 mL/min to 150 mL/min (upper limit in PopPK analysis). Creatinine clearance was also linearly correlated with ideal body weight in this population. Ideal body weight adjusted apparent clearance of hydroxybupropion, threohydrobupropion, and erythrobupropion showed a shallow increase with increasing creatinine clearance. The ideal body weight adjusted clearance showed linear increase for 6β-naltrexol with increasing creatinine clearance. This suggests that with decreasing renal function these metabolites accumulate to relatively greater extent in comparison to that under normal renal function.

2.3.3 Does the hepatic function affect NB pharmacokinetics?

Effect of hepatic impairment was not evaluated for Contrave. Naltrexone is known to have extensive first-pass metabolism to 6β-naltrexol (non-CYP mediated pathway), bupropion is metabolized to hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Both parent drugs and their metabolites also undergo conjugation in liver. Adequate studies of naltrexone in patients with hepatic impairment have not been conducted. Based on the bupropion product labels, there is lack of systematic evaluation of bupropion in hepatic impaired. However, the available data suggests that bupropion exposure could be higher (3-fold higher AUC in severe hepatic cirrhosis) and metabolites also had increased exposures in comparison to healthy subjects.

2.4 Extrinsic Factors

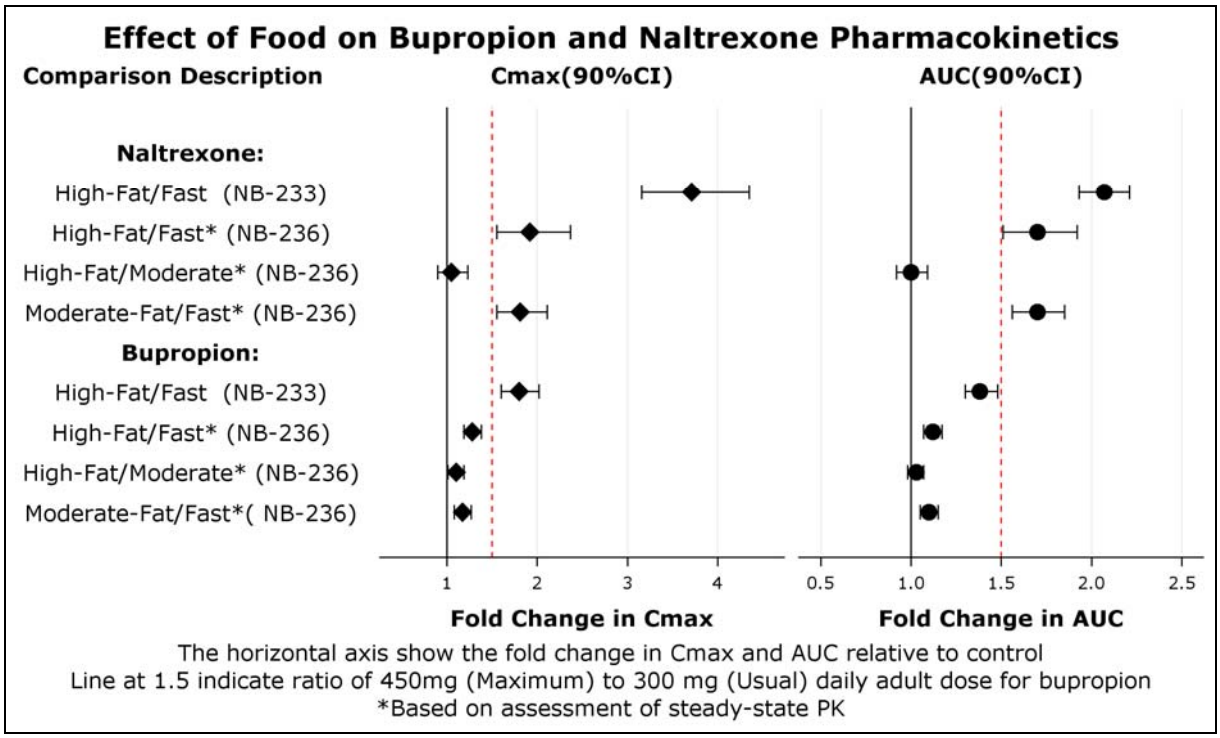
2.4.1 What is the effect of food on the bioavailability of NB?

Single dose food effect:

Single oral dose food effect study showed that when given with high-fat diet, naltrexone peak and total exposure were increased to >1.5 fold numerically exceeding those expected from 48 mg total daily dose. However, bupropion peak and total exposure were increased in clinically alarming way in the presence of high-fat diet with fold increase in Cmax greater than 1.5.

The results of single and steady-state food effect studies are summarized in Figure 25 below.

Figure 25 Effect of food on naltrexone and bupropion exposure from Contrave



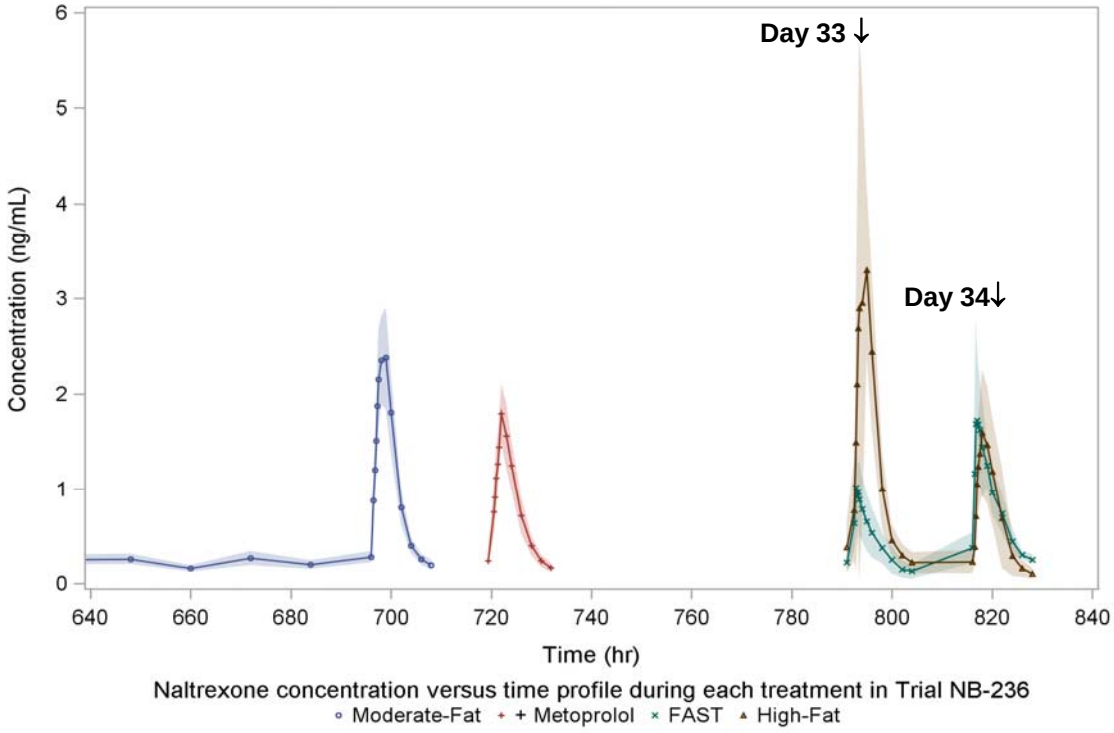
Steady-state food effect:

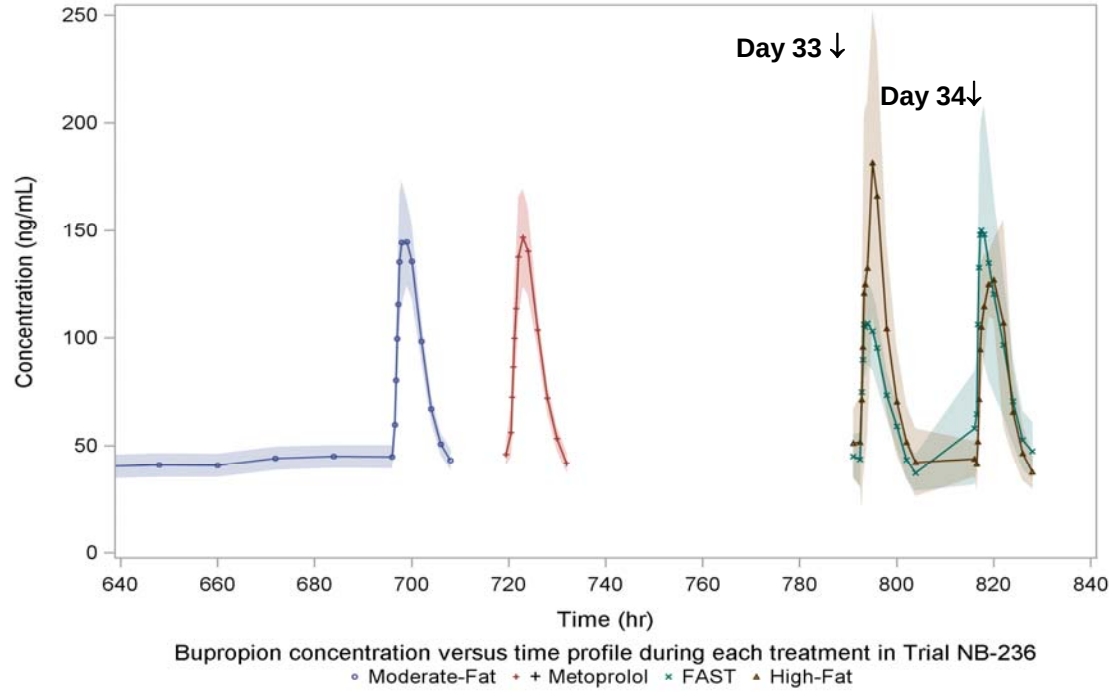
Steady-state PK parameters were assessed after administering NB 8/90 mg with moderate fat diet (up to Day 30). This was followed by DDI assessment with SD metoprolol on Day 31. During the optional extension phase post-day 31 subset of subjects (n=11) were randomized to either receive morning doses on Day 33 and 34 under fasted or high-fat diet in a crossover fashion, while evening doses on Day 33 were given under fed condition.

Effect of high-fat diet at steady-state had similar direction as that of single dose evaluation on both naltrexone and bupropion when compared to the fasted state. However, the magnitude of effect was lower than that observed under single dose setting. Effect of moderate-fat diet was slightly lower in magnitude than that of high-fat; the direction of effect was similar for both naltrexone and bupropion components.

However, the results of this steady-state food effect study have some limitations; first, inherently this study design is less sensitive in revealing the effect of food on the release profile of formulation in comparison to a single dose food effect study. Second, the study design did not test if the altered conditions post Day 30 would attain a different steady-state in comparison to the baseline moderate-fat fed condition, as the single administration on Day 33 or Day 34 in a cross-over fashion does not allow for this assessment. Third, the effect on exposure of fed and fasted was not consistent on Days 33 and 34 when plotted on real-time scale (see Figure 26 below) and the reason for this is not apparent. Therefore, at best the only thing that can be inferred from the ratio of Cmax and AUCs from this trial is the expected fluctuation in exposure due to change in diet pattern.

Figure 26 Effect of food on naltrexone and bupropion exposure from Contrave at steady-state





The food was not restricted in the Phase 3 trials; however, the time of administration with respect to food was not recorded. Though, exposure-response analysis using the trough bupropion concentrations for TEAEs did not reveal any relationship for Psychiatric AEs and increasing

bupropion concentrations in Phase 3 trial NB-303. There were only 2 seizure events in the Contrave clinical program and patients with history of seizures were excluded and therefore dose-response or exposure-response for this AE is not feasible from the available data.

According to the Wellbutrin SR label:

(http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018644s038,020358s045lbl.pdf)

"**Bupropion is associated with seizures in approximately 0.4% (4/1,000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as 4-fold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for WELLBUTRIN increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg)….**

…..The risk of seizure appears to be strongly associated with dose. Sudden and large increments in dose may contribute to increased risk."

Considering the nature of dose response for bupropion, there is no room for higher bupropion exposure based on the known safety concerns for abrupt increase in seizure frequency above 450 mg total daily bupropion dose (1.5 fold). With regards to naltrexone, the available data shows lack of benefit from naltrexone doses above 32 mg.

Therefore, from clinical pharmacology perspective Contrave should not be taken with high-fat diet.

2.4.2 Drug-Drug Interactions

2.4.2.1 What is the CYP inhibition potential of NB?

The hepatic metabolism of bupropion as well as the effects of bupropion and its metabolites on CYP enzymes in humans is relatively well understood. Bupropion and hydroxybupropion are known inhibitors of CYP2D6 isoenzyme *in vitro*. Therefore, *in vitro* evaluations were not performed for bupropion component of CONTRAVE.

The *in vitro* enzyme inhibition studies conducted with naltrexone and its major metabolite, 6β-naltrexol using human liver microsomes demonstrate that:

- **Naltrexone** produced no direct or time-dependent inhibition of human microsomal CYP1A2, 2A6, 2B6, 2C8, 2E1, or 3A4.
- The activity of CYP2C9 was slightly inhibited by approximately 16% for direct inhibition, and CYP2C19 was moderately inhibited by approximately 20% for direct inhibition or 40% with 30 minute pre-incubation, respectively. No IC50 values for the inhibition of CYP2C9 or 2C19 could be calculated because of the negligible inhibition which only occurred at the highest concentration tested (50 μM, but not at 10 μM or lower).
- Inhibition of CYP2D6 activity by approximately 56% or 59% was observed with 50 μM naltrexone directly or after 30 minutes of pre-incubation, with IC50 values of 39 μM and 31 μM respectively.
- These *in vitro* findings for inhibition of CYP2C9, 2C19, and 2D6 with 50 μM naltrexone are likely to have no clinical relevance given that this naltrexone concentration is >6000-

fold higher than the observed mean Cmax (approximately 2.7 ng/mL or 0.008 μM) following steady-state administration of NB 8/90 tablets in Study NB-236.

- **6β-naltrexol** produced no direct inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4.
- With a 30 min pre-incubation CYP2C19 activity was modestly decreased (approximately 20%), only at the highest 6β-naltrexol concentration of 50 μM.
- 6β-naltrexol results are not likely to be clinically relevant given that only modest inhibition was seen at concentrations >300-fold higher than the observed 6β-naltrexol Cmax value (approximately 52 ng/mL or 0.15 μM) following administration of two NB 8/90 tablets to steady state in Study NB-236.

The *in vitro* enzyme induction studies conducted with naltrexone and its major metabolite, 6β-naltrexol using human liver microsomes demonstrate that:

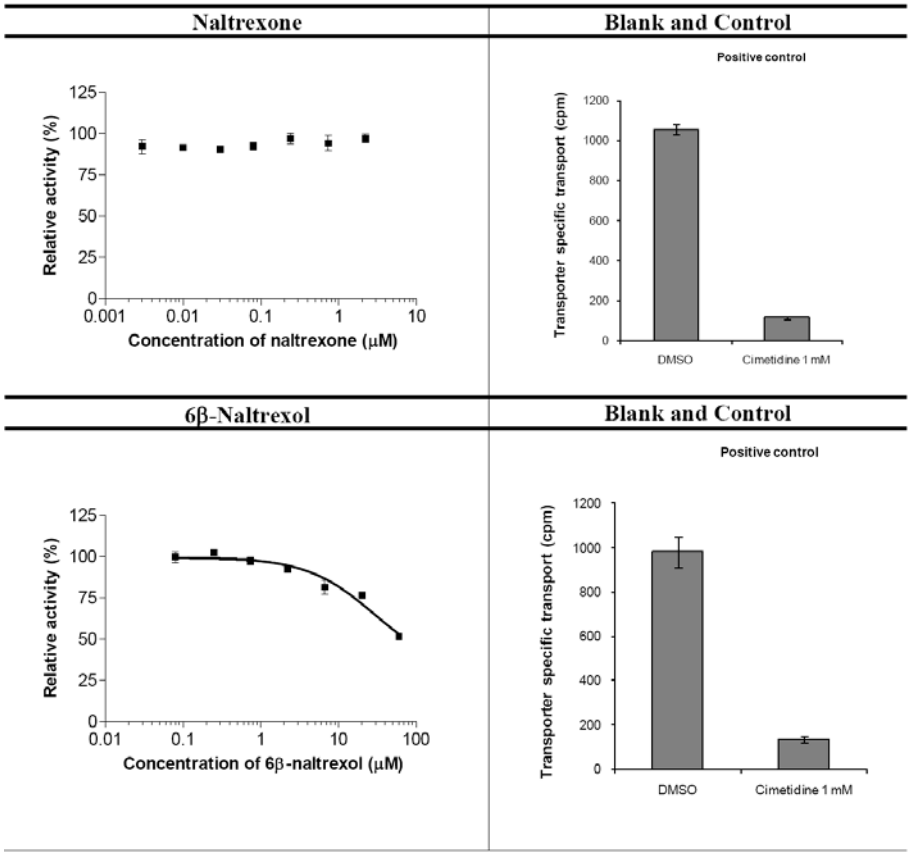
- Both naltrexone and 6β-naltrexol produced little change (<20%) in the activity of CYP1A2, CYP2B6, or CYP3A4 in comparison to that observed with positive controls (omeprazole, phenobarbital, and rifampin, respectively). This change in the activity of CYP1A2, CYP2B6, or CYP3A4 was only evident at the highest concentration tested (50 μM) and therefore have little potential for inducing these drug metabolizing enzymes.

Thus, naltrexone component of CONTRAVE is not expected to cause any drug-drug interactions related to inhibition/induction of cytochrome P450s.

2.4.2.2 What is the inhibition potential of naltrexone and bupropion at human Organic Cation Uptake Transporters (OCTs)?

Chinese Hamster Ovary (CHO) cells expressing human OCT2 were analyzed for inhibition of metformin uptake by naltrexone and its metabolite 6β-naltrexol, also by bupropion and its metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Naltrexone and 6β-naltrexol showed no clinically relevant potential for interference with the human OCT2 uptake transporter. Naltrexone did not inhibit the human OCT2-mediated metformin uptake, and 6β-naltrexol showed only modest dose-dependent inhibitory effect at the highest concentration (Figure 27).

Figure 27 Inhibition of OCT2 transporter measured in OCT2 uptake inhibition assay



The IC50 value for 6β-naltrexol could not be determined in the investigated drug concentration range as the maximum observed inhibition was only approximately 50% at the highest concentration tested which exceeded clinical Cmax values by ~300-fold.

Table 12 Calculated parameters of TAs from the drug total and free concentrations in humans and from IC50 values

Test Analyte	Cmax, total (µM) *	Cmax, total /IC50	TA protein binding (%)**	Cmax, free (µM)	Cmax free /IC50
Naltrexone	0.0079	-	21	0.006	-
6β-Naltrexol	0.192	0.0032***	21	0.151	0.0025***

*maximum concentration of analyte after oral administration
**assuming 6β-naltrexol has equal plasma protein binding
***assuming IC_{50} value of 60 µM
Cimetidine, bupropion and bupropion metabolites inhibited the uptake of metformin mediated by human OCT2 in a dose-dependent manner. Maximal inhibition values were 92.50% and 88.77%, respectively (Figure 28).

Figure 28 Inhibition of OCT2 transporter by cimetidine and bupropion measured in OCT2 uptake inhibition assay

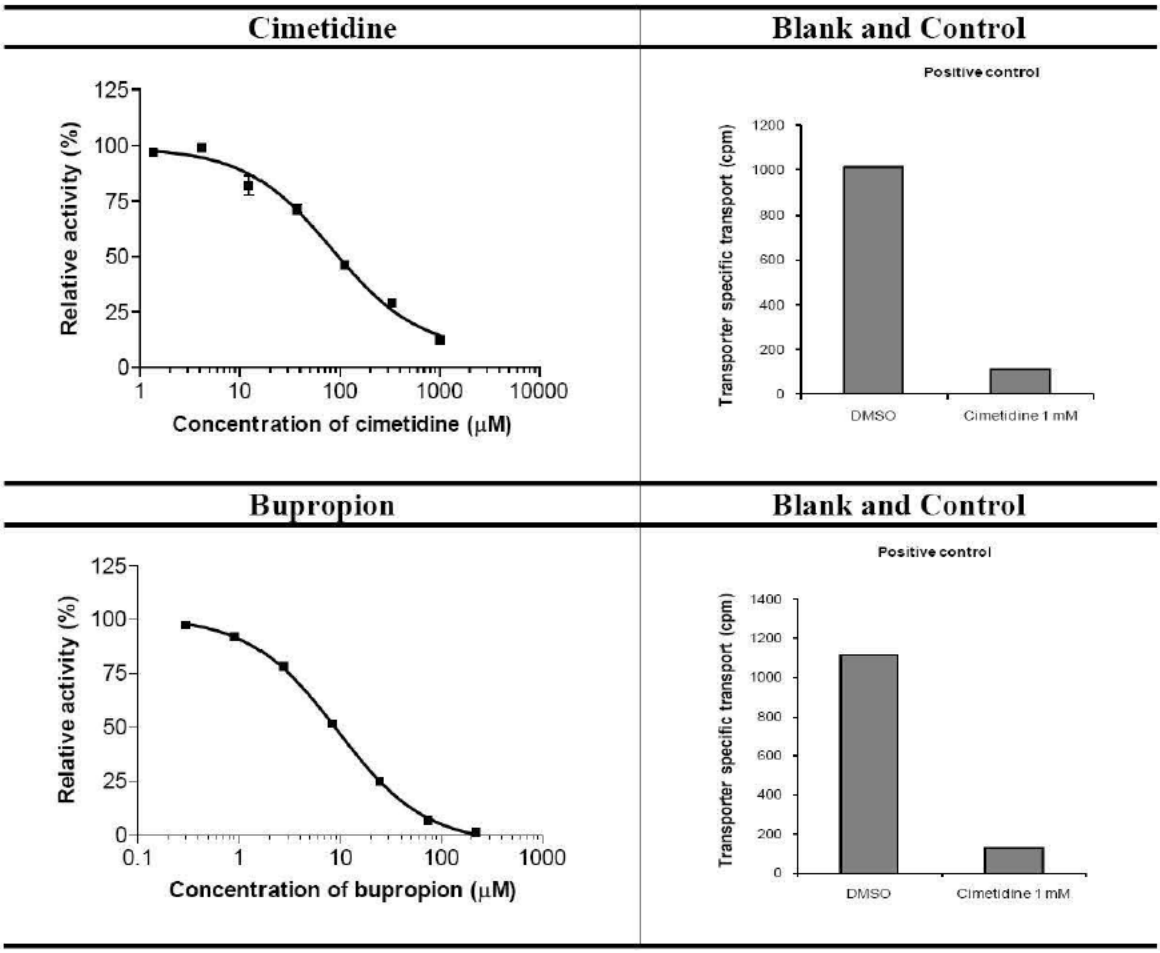
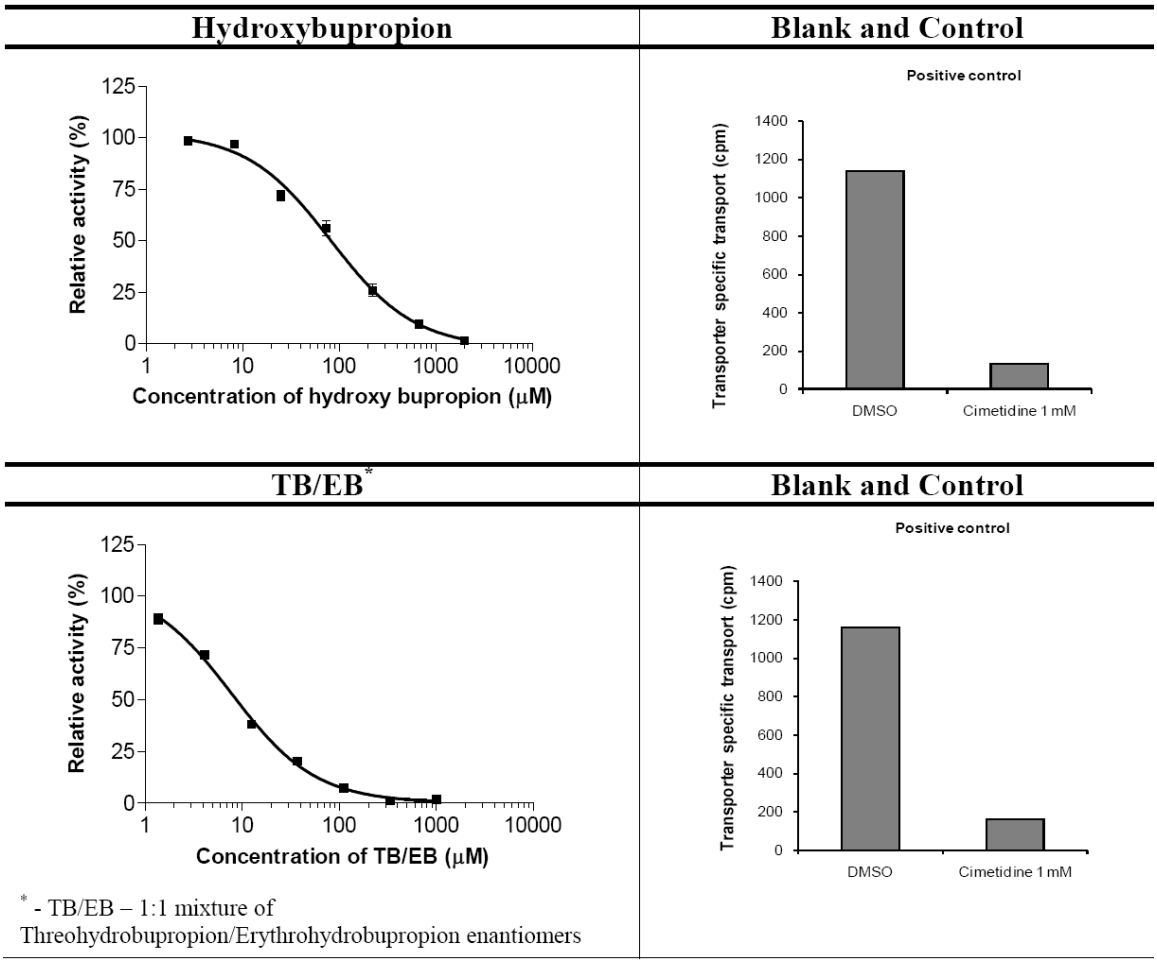


Figure 29 Inhibition of OCT2 transporter by hydroxybupropion and threohydrobupropion/ erythrohydrobupropion mixture measured in OCT2 uptake inhibition assay



* - TB/EB – 1:1 mixture of Threohydrobupropion/Erythrohydrobupropion enantiomers

Table 13 Calculated reaction parameters from OCT2 uptake inhibition assay

TA	Maximal inhibition (%)*	IC_{50} (μM)
Cimetidine	92.50	83.33
Bupropion	100.00	9.28
Hydroxybupropion	100.00	81.63
TB/EB**	99.78	7.78

* calculated from the equation of the fitted curve at the highest TA concentrations
**TB/EB –mixture of Threohydrobupropion/Erythrohydrobupropion enantiomers

Table 14 Calculated parameters of TAs from the drug total and free concentrations in humans and from IC50 values

TA	Dose/day	Cmax total (µM) *	TA plasma protein binding (%)	Cmax free (µM)	Cmax total /IC50	Cmax free /IC50
Cimetidine	400 mg	11.8	25	8.85	0.14	0.11
Bupropion	360 mg	0.667	84	0.107	0.07	0.01
Hydroxybupropion		6.882	84	1.101	0.08	0.01
TB/EB**		3.917	42	2.272	0.5	0.29

*maximum concentration of analyte after BID oral administration of 180 mg (2 x NB 8/90 mg) or 400 mg cimetidine single dose

***1:1 mixture of Threohydrobupropion/Erythrobupropion enantiomers, thus Cmax is a sum of two individual Cmax values

Bupropion and its metabolites showed nearly 100% inhibition of the OCT2 transporter at the highest concentrations tested, which were generally ~300-fold greater than steady state Cmax concentrations, although the individual enantiomers in the TB/EB mixture ranged from ~150-fold for TB to ~750-fold for EB).

The ratio of the free (unbound) Cmax and IC50 value was calculated in order to predict clinical relevance of in vitro findings. In general, drugs exhibiting equal or higher than 0.1 Cmax, free/IC50 ratio presumably exhibit clinical inhibition. The Cmax, free/IC50 ratio for bupropion and hydroxybupropion were well below this threshold, but the ratio for the TB/EB metabolite mixture was 0.29, suggesting that clinically relevant interaction through inhibition of OCT2 could occur at therapeutic bupropion doses.

2.4.2.3 What is the effect of co-administered drugs on the pharmacokinetics of naltrexone and bupropion from Contrave formulation?

Clinical DDI investigations were conducted at the highest recommended dose (two NB 8/90 tablets given once for single dose studies, or twice daily (BID) for the multiple dose study) with representative medications from anti-hypertensive, anti-diabetic and lipid-lowering classes. Co-administration of various representative drugs did not affect the exposure of naltrexone or bupropion in a clinically meaningful way (See Figure 30 and 31 below). The least square mean ratios were close to one and 90% confidence intervals were contained within the 0.8 to 1.25 interval. The results with glyburide were confounded with the food effect due to oral glucose solution that was co-administered. Oral glucose solution is known to affect the gastro-intestinal motility.

Figure 30 Effect of co-administered drugs on the naltrexone pharmacokinetics

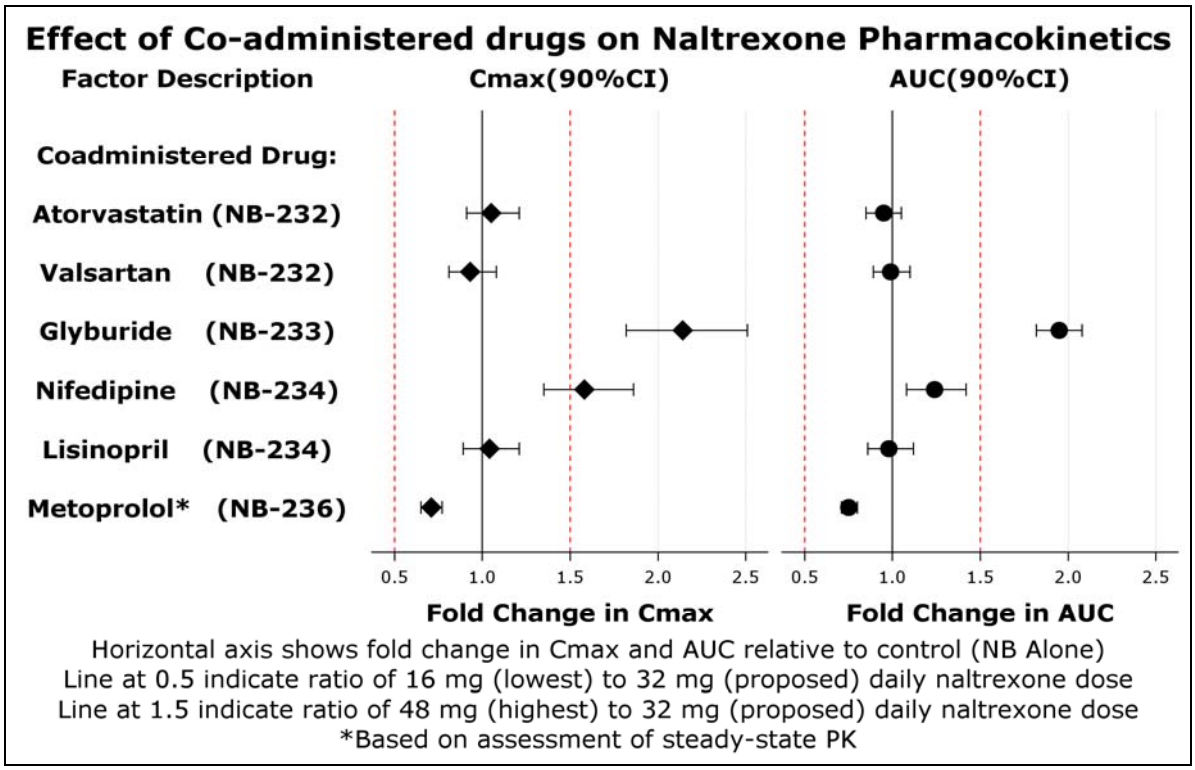
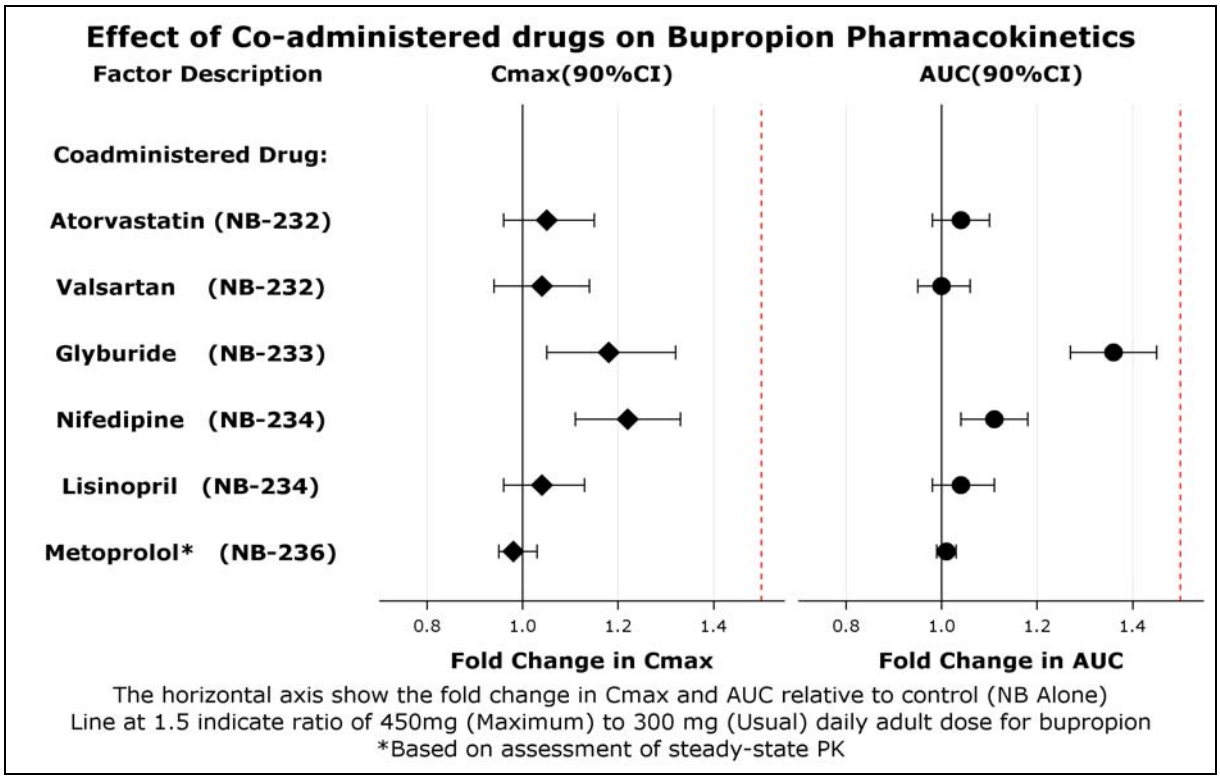


Figure 31 Effect of co-administered drugs on bupropion pharmacokinetics



2.4.2.2 What is the effect of Contrave co-administration on the pharmacokinetics of other drugs?

Drug-drug interaction (DDI) studies in the Contrave development program were conducted with the primary objective of evaluating the effect of co-administered drugs (atorvastain, valsartan, glyburide, nifedipine, lisinopril, and metoprolol) on the pharmacokinetics of naltrexone and bupropion components. The treatment arm of co-administered drug given alone was not included in any study except in the DDI study with metoprolol. All other studies compared the pharmacokinetic data collected after co-administration with Contrave to that reported in literature or in approved product labels. This cross-study comparison is only acceptable for signal detection from clinical pharmacology perspective and cannot be relied upon for establishing or ruling out a DDI. The cross-study comparison do not signal for any meaningful changes in the exposure of the co-administered drugs due to Contrave; atorvastain, valsartan, glyburide, nifedipine and lisinopril.

Co-administration of single metoprolol dose at steady-state of Contrave resulted in 2 fold (90% CI 1.73 – 2.45) increase in Cmax and 4 fold increase (90% CI 3.33 – 5.33) in AUC of metoprolol. This study was conducted in subjects genotyped as extensive CYP2D6 metabolizers to ensure that results are not confounded by the poor baseline metabolic capacity of poor metabolizers.

Table 15 Effect of Contrave on metoprolol pharmacokinetics

Plasma Metoprolol Pharmacokinetic Parameters	Day 1 Mean ± SD (n = 18)	Day 31 Mean ± SD (n = 17)	%GMR (90% CI)
C_{max} (ng/mL)	71.7 ± 30.4	141 ± 33.8	205.64 (172.77 - 244.77)
T_{max} (hr)	1.50 (0.75, 4.01)	2.00 (0.76, 3.00)	
$t_{½}$ (hr)	3.61 ± 0.99	6.61 ± 0.94	
AUC_{0-t} (ng*hr/mL)	397.80 ± 340.19	1242.36 ± 292.47	379.54 (299.61 - 480.78)
$AUC_{0-\infty}$ (ng*hr/mL)	411.30 ± 366.12	1410.83 ± 337.41	421.14 (332.72 - 533.07)

Day 1 = 1 metoprolol 50 mg IR tablet QD (fed)
Day 31 = 2 naltrexone SR 8 mg/bupropion 90 mg SR trilayer tablets BID + 1 metoprolol 50 mg IR tablet QD (fed)
T_{max} presented as Median (Minimum, Maximum)
AUC_{0-t} represents area under the curve from time 0 to time of last quantifiable concentration, up to 24 hours postdose.

2.5 General Biopharmaceutics

2.5.1 Is bioequivalence established between the to-be-marketed formulation and the Phase 2/3 trial formulation and how does it relate to the overall product development?

Phase 2 studies in which obese patients were treated with combinations of naltrexone HCl and bupropion HCl (referred to in this section as naltrexone and bupropion) were conducted with separate dosage forms of naltrexone and bupropion that were obtained from commercial sources or developed as investigational formulations. Prior to the start of the Phase 3 program, a tablet containing both naltrexone and bupropion was developed by the sponsor and selected as the final intended commercial drug product. This tablet was (b) (4) Drug product manufactured by (b) (4) accounted for the majority of Phase 3 dosing (including all dosing in Studies NB-301 and NB-303), as well as all key clinical pharmacology studies, and was therefore considered the pivotal

clinical trial material. Only minor modifications to the drug product manufacturing process [redacted] occurred after initiation of Phase 3. In the case of bupropion, [redacted] In the case of naltrexone, [redacted] The tablet was manufactured under [redacted] as presented in Table 16 and [redacted]. The main differentiation between these schemes is as follows:

[redacted]

Table 16 Manufacturing schemes used for Contrave formulation dusing the development

[redacted]

The formulations and reference products studied over the course of the clinical program are summarized in Table 17. All pivotal Phase 3 studies (NB-301, NB-302, NB-303 and NB-304) as well as key clinical pharmacology studies of drug-drug interactions, of the effect of food, and those to evaluate the PK performance of developmental formulations against approved formulations (NB-230, NB-232, NB-233, NB-234 and NB-236) utilized the intended commercial formulation.

Table 17 Details of formulations utilized in various clinical trials

Study Identifier	Objective	Naltrexone, Bupropion or Combination Formulations				
		Nal IR	Nal SR	Bup SR	Trilayer Tablet	Monolayer Tablet
IR-PET	Receptor Occupancy	√				
NB-222	Receptor Occupancy		√			
OT-101, NB-201	Phase 2 Efficacy	√		√		
NB-221	Comparative PK	√	√			
NB-225[a]	Comparative PK	√	√	√		
NB-228[b], NB-229[c]	Relative BA of Tablets Manufactured according to Different Schemes				√	
NB-230	Relative BA of NB 8/90 Tablets to Approved Formulations	√		√	√	
NB-231, NB-237 NB-238	Relative BA of Monolayers to NB 8/90 Tablets				√	√
NB-232, NB-233 NB-234, NB-236	Drug-drug Interaction (All) and Food Effect (NB-233 & -236)				√	
NB-239	Relative BA of Monolayers to NB 8/90 Tablets and Food Effect				√	√
NB-301, NB-302, NB-303, NB-304	Phase 3 Efficacy				√	
NB-401, NB-402	Open label Phase 2				√	
NB-431	Phase 2 fMRI				√	

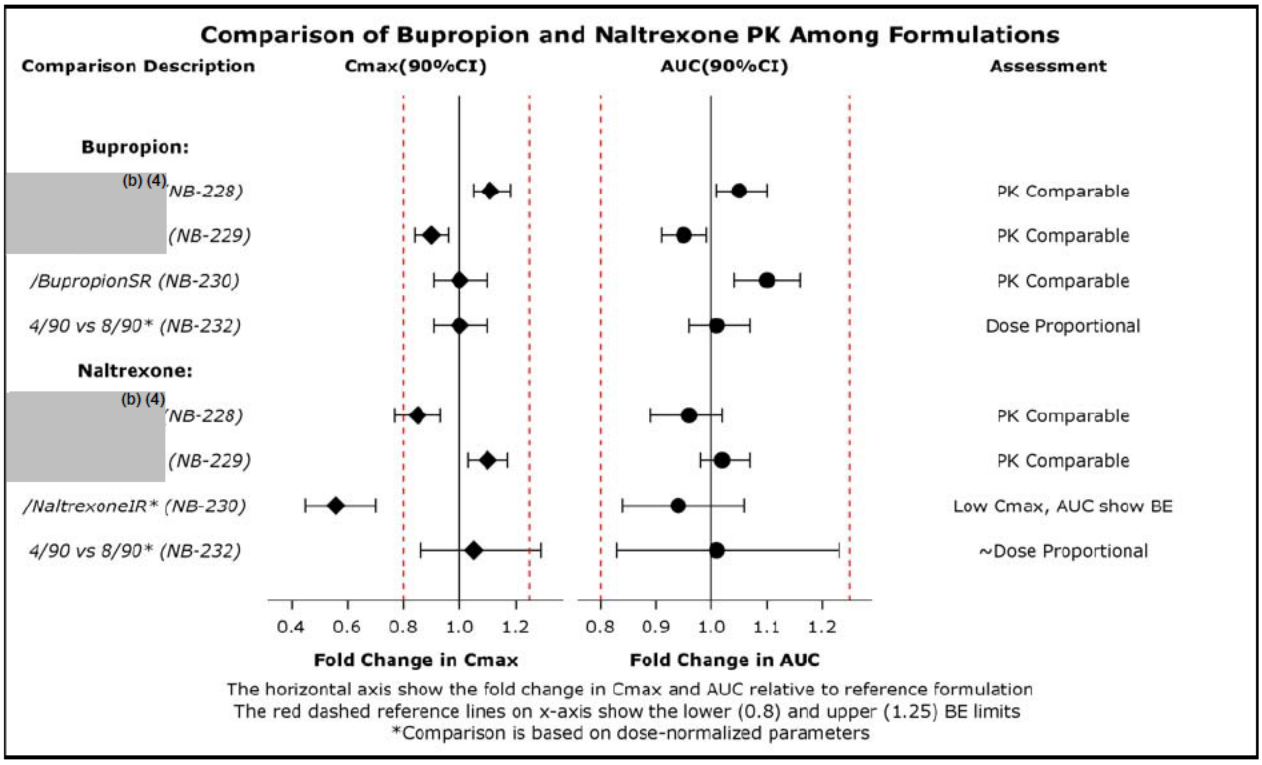
[a]Nal IR (12 mg) or Nal SR (12.5 mg) was combined with with Bup SR (90 mg) in a single capsule

(b) (4)

Abbreviations: fMRI= functional magnetic resonance imaging; IR= immediate-release; PK= pharmacokinetics; SR= sustained-release; BE= bioequivalence; BA= bioavailability; Nal= naltrexone; Bup= bupropion

Summary of various bioequivalence assessments carried out for various stages of Contrave formulation development is presented in Figure 32.

Figure 32 **Summary of BE evaluations conducted for the formulations utilized during clinical development including the intended commercial formulation**



Based on the results of statistical analyses it can be concluded that:

- NB formulations were bioequivalent with respect to the primary endpoints $AUC_{0\text{-}inf}$ and C_{max} except for one case where (b) (4) formulation did not show bioequivalence to (b) (4) with regards to naltrexone C_{max}, while the naltrexone $AUC_{0\text{-}inf}$ was comparable.
- NB 8/90 mg formulation was bioequivalent to bupropion SR 150 mg with respect to the primary endpoints $AUC_{0\text{-}inf}$ and C_{max}, though $AUC_{0\text{-}inf}$ was 10% higher than the Bupropion SR 150 mg.
- NB 8/90 mg formulation was not bioequivalent to naltrexone IR 50 mg with respect to the primary endpoints $AUC_{0\text{-}inf}$ and C_{max}, this was expected based on lower dose of naltrexone (16 mg) used.

2.6 Analytical

2.6.1 Is the analytical method for NB appropriately validated?

Bioanalysis of naltrexone, bupropion and their respective metabolites was conducted using plasma samples obtained from clinical pharmacology and safety/efficacy studies. Assays for determination of plasma concentrations of metoprolol, lisinopril, glyburide, valsartan, nifedipine, and atorvastatin (and its hydroxyl metabolites) were used in support of drug-drug interaction studies. All analytes were quantitated using high performance liquid chromatographic (HPLC) tandem mass spectrometry (LC/MS/MS) methods.

An overview of the various assays used for each clinical study is presented below in Table 18.

Table 18 Summary of analytical method used for the CPB studies

Method Description	Clinical Study Sample Analysis[a,b]	Method Validation Report
Naltrexone and 6β-naltrexol (1 to 100 ng/mL)	Naltrexone: PET-IR, NB-221 6β-naltrexol: PET-IR, NB-221, NB-222, NB-225, NB-228	(b) (4) Project Number 060106
Naltrexone (20 to 2000 pg/mL)	NB-222, NB-225, NB-228	(b) (4) Project Number 080314
Naltrexone (20 to 2000 pg/mL) and 6β-naltrexol (100 to 10,000 pg/mL)	NB-303[c]	(b) (4) Project Number 080502
Naltrexone (20 to 2000 pg/mL) and 6β-naltrexol (100 to 10,000 pg/mL)	NB-303	(b) (4) Report Number 87133
Naltrexone (0.0200 to 2.00 ng/mL) and 6β-naltrexol (0.500 to 50.0 ng/mL)	NB-229, NB-230, NB-231, NB-232, NB-233, NB-234, NB-236, NB-237, NB-238, NB-239	(b) (4) Report Number (b) (4) 08-253
Bupropion (1 to 200 ng/mL), hydroxybupropion (5 to 1000 ng/mL), threohydrobupropion (1 to 200 ng/mL), erythrohydrobupropion (1 to 40 ng/mL)	NB-225, NB-228	(b) (4) Report Number 35068 Original Validation SOP (b) (4) 8571
Bupropion (1 to 500 ng/mL), hydroxybupropion (5 to 5000 ng/mL), threohydrobupropion (5 to 2500 ng/mL), erythrohydrobupropion (1 to 500 ng/mL)	NB-303	(b) (4) Report Number 35068 Partial Validation 7 SOP (b) (4) 9696
Bupropion, hydroxybupropion, threohydrobupropion, erythrohydrobupropion (1 to 1000 ng/mL)	NB-229, NB-230, NB-231, NB-232, NB-233, NB-234, NB-236, NB-237, NB-238, NB-239	(b) (4) Report Number (b) (4) 08-258
Metoprolol (0.5 to 250 ng/mL)	NB-236	(b) (4) Report Number (b) (4) 06-115
Lisinopril (0.50 to 250.50 ng/mL)	NB-232	(b) (4) Report Number 65129 Partial Validation 2
Glyburide (2 to 400 ng/mL)	NB-233	(b) (4) Study Number ZZ17229-01
Valsartan (50.0 to 10,000 ng/mL)	NB-232	(b) (4) Report Number (b) (4) 07-115
Nifedipine (1 to 250 ng/mL)	NB-234	(b) (4) Report Number (b) (4) 08-274
Atorvastatin, para-Hydroxy Atorvastatin and ortho-Hydroxy Atorvastatin (0.300 to 50.0 ng/mL)	NB-234	(b) (4) Labs Report Number (b) (4) 08-367

[a]Lower sensitivity assay was used originally for NB-222, NB-225 and NB-228 analysis. Naltrexone results from these studies were not quantifiable in ~2/3 of the samples; therefore all sample analysis was repeated and replaced by data from a higher sensitivity assay.

[b]Metabolite concentrations were not determined in studies NB-231, NB-237, and NB-238.

[c]The (b) (4) analysis site (b) (4) was closed during conduct of NB-303. Results generated by (b) (4) were reported by (b) (4) and sample analysis and reporting of remaining samples were conducted by (b) (4)

An overview of the performance of various assays is presented below in Table 19. The assay methods are briefly described for naltrexone and bupropion components below:

1. Tandem Method for the Analysis of Naltrexone and 6β-Naltrexol in Human Plasma

A liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method of analysis was used for determining naltrexone and 6β-naltrexol concentrations in human plasma (K2EDTA). This method was validated with a quantitation range of 0.02 to 2.00 ng/mL for naltrexone and 0.50 to 50.0 ng/mL for 6β-naltrexol. Naltrexone and 6β-naltrexol and the internal standards, Naltrexone-d3 and 6β-naltrexol-d4, were isolated from human plasma using a liquid/liquid extraction procedure. The method was originally validated using naloxone as the internal standard. The data to support this change is reported with the validation. For naltrexone, a linear regression with $1/x^2$ weighting was used to obtain the best fit of the data for the calibration curves. Quality control (QC) samples at concentrations of 0.06 ng/mL (low (L) QC), 0.80 ng/mL (medium (M) QC) and 1.60 ng/mL (high (H)QC) for naltrexone, prepared in human plasma, were analyzed to establish assay precision and accuracy.

For 6β-naltrexol, a quadratic regression with 1/x weighting was used to obtain the best fit of the data for the calibration curves. QC samples at concentrations of 1.50 ng/mL (LQC), 20.0 ng/mL (MQC) and 40.0 ng/mL (HQC) for 6β-naltrexol, prepared in human plasma, were analyzed to establish assay precision and accuracy.

During validation (with naloxone as the internal standard), intra-day and inter-day precision and accuracy were evaluated from the results of the QC samples processed in three separate batch runs. The intra-day precision and accuracy of QC samples in three separate batch runs were within 15% for naltrexone and within 10% for 6β-naltrexol. The inter-day precision and accuracy of the QC samples were within 7% for naltrexone and 6% for 6β-naltrexol.

2. Tandem Method for the Analysis of Bupropion and its Active Metabolites in Human Plasma

An LC/MS/MS method of analysis was used for determining bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion concentrations in human plasma (K2EDTA). This method was validated with a quantitation range of 1.00 to 1,000 ng/mL. Bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion and the internal standards, bupropion-d9, hydroxybupropion-d6 and rac threohydrobupropion-d9, were isolated from human plasma using a solid-phase extraction procedure.

Quadratic regression with $1/x^2$ weighting was used to obtain the best fit of the data for the calibration curves. QC samples at concentrations of 3.00 ng/mL (LQC), 400 ng/mL (MQC) and 800 ng/mL (HQC), for bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion, prepared in human plasma, were analyzed to ensure acceptable assay data to support this change is reported with the validation. During validation, intra-day and inter-day precision and accuracy were evaluated from the results of the QC samples processed in three separate batch runs for bupropion and four separate batch runs for hydroxybupropion, threohydrobupropion and erythrohydrobupropion. The intra-day precision and accuracy of QC samples were within 12% and 18%, respectively for all analytes. The inter-day precision and accuracy of the QC samples were within 13% and 8%, respectively for all analytes.

Two bioanalytical sites [redacted] (b) (4) were used for naltrexone and 6β-naltrexol sample analysis from Study NB-303. Population pharmacokinetic analysis combined Phase 3 results from these two sites as well as Phase 1 study

results quantitated by a different bioanalytical site (b) (4). Studies were performed to show that the naltrexone analysis at (b) (4) produced similar results, and that results for naltrexone and bupropion (and their metabolites) were similar at (b) (4)

NB-303 study samples were initially analyzed at (b) (4). After the announcement of the facility closure, all samples were transferred to (b) (4) to continue study sample analyses. Before continuing the analysis at (b) (4) an inter-laboratory cross-validation with the bioanalytical methodology used by (b) (4) to support the naltrexone and 6β-naltrexol in human sodium heparinized plasma analysis was performed. Forty study samples previously analyzed at (b) (4) were reanalyzed using the (b) (4) validated method for naltrexone and 6β-naltrexol in human sodium heparinized plasma. Comparability required at least 67% of the repeat samples to be within 20% of the originally reported data. A total of 93.75% of the repeat sample results were within the originally reported values for naltrexone and 100% of the repeat samples results were within the originally reported values for 6β-naltrexol, demonstrating the assays at the two sites performed similarly.

These results indicated that the intra-day and inter-day precision and accuracy were satisfactory for determination of naltrexone, 6β-naltrexol, bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion in plasma and the methods were adequately validated. The analytical ranges for these analytes (including the dilution factors) used were sufficient to cover the observed concentrations in the clinical studies.

Table 19 Performance summary of analytical method used for the CPB studies

Analyte(s)	Range (extended; DF)	Intra-Assay		Inter-Assay		Report Number
		Precision (QC CV)	Accuracy (QC % bias)	Precision (QC CV)	Accuracy (QC % bias)	
Naltrexone	1 - 100 ng/mL (150 ng/mL; 2X)	1.87 to 3.86%	-3.31 to 4.40%	4.07 to 4.89%	-6.41 to -1.38%	(b) (4) Project Number 060106
Naltrexol	1 - 100 ng/mL (150 ng/mL; 2X)	2.78 to 3.61%	3.07 to 13.35%	5.22 to 6.64%	-3.50 to 2.48%	
Naltrexone	20 - 2,000 pg/mL (6,000 pg/mL; 4X)	2.34 to 4.52%	-6.81 to 0.26%	2.07 to 3.41%	-6.31 to 2.16%	(b) (4) Project Number 080314
Naltrexone	20 - 2,000 pg/mL (6,000 pg/mL; 4X)	1.66 to 4.08%	-5.34 to-0.26%	2.79 to 5.79%	-5.96 to -4.63%	(b) (4) Project Number 080502
Naltrexol	100-10,000 pg/mL (30,000 pg/mL; 4X)	0.71 to 2.13%	-0.46 to 2.22%	2.46 to 3.64%	-0.29 to 0.23%	
Naltrexone	19.88 – 1988.00 pg/mL (3979.60 pg/mL; 20X)	2.01 to 13.48%	-9.29 to -0.36 %	2.55 to 11.02%	-2.87 to -1.02	(b) (4) Report Number 87133
6β-Naltrexol	100.00 – 50,000.00 pg/mL (100,000 pg/mL; 20X)	1.13 to 9.86%	-7.43 to -5.79%	2.10 to 7.44%	-6.48 to -3.27%	
Naltrexone	0.0200 to 2.00 ng/mL (8.00 ng/mL; 10X)	1.7 to 6.4%	-5.6 to 5.0%	2.8 to 5.0%	-2.0 to 1.3%	(b) (4) Project Number (b) (4) 08-253
6β-Naltrexol	0.500 to 50.0 ng/mL (200 ng/mL; 10X)	1.2 to 9.8%	-3.0 to 4.0%	0.0 to 3.5%	-1.0 to 0.7%	
Bupropion	1.00 – 1,000 ng/mL (4,000 ng/mL; 10X)	1.8 to 6.7%	-10.9 to -1.0%	2.9 to 3.4%	-7.1 to -4.3%	(b) (4) Report Number (b) (4) 08-258
Hydroxybupropion	1.00 – 1,000 ng/mL (4,000 ng/mL; 10X)	1.6 to 7.8%	-7.4 to 4.7%	2.0 to 4.9%	-0.1 to 1.3%	
Threohydrobupropion	1.00 – 1,000 ng/mL (4,000 ng/mL; 10X)	2.4 to 7.2%	-4.4 to 1.3%	0.0 to 2.0%	-2.3 to -1.3%	
Erythrohydrobupropion	1.00 – 1,000 ng/mL (4,000 ng/mL; 10X)	1.5 to 7.1%	-7.4 to 2.3%	0.0 to 3.8%	-2.0 to -0.8%	
Bupropion	1 to 200 ng/mL (20X)	1.26 to 4.27%	88.78 to 93.48*%	3.45 to 4.17%	92.71 to 97.06*%	(b) (4) original validation Project Number 35068 SOP (b) 8571
Hydroxybupropion	5 to 1000 ng/mL (20X)	3.47 to 8.03%	99.67 to 103.22*%	4.76 to 5.75%	95.10 to 99.87*%	
Threohydrobupropion	1 to 200 ng/mL (20X)	1.44 to 7.14%	95.25 to 100.10*%	3.10 to 4.55%	95.09 to 98.92*%	
Erythrohydrobupropion	1.00 to 40 ng/mL (20X)	2.96 to 8.01%	96.92 to 105.22*%	2.93 to 4.99%	97.77 to 99.90*%	

Table 19 Continued

Analyte(s)	Range (extended; DF)	Intra-Assay		Inter-Assay		Report Number
		Precision (QC CV)	Accuracy (QC % bias)	Precision (QC CV)	Accuracy (QC % bias)	
Bupropion	1 to 500 ng/mL (20X)	1.49 to 7.52%	-2.34 to 10.90%	2.66 to 4.70%	-1.35 to 2.20%	(b) (4) Project Number 35068 Partial Validation 7 SOP (b) (4) 9696
Hydroxybupropion	5 to 5000 ng/mL (20X)	0.93 to 3.33%	-3.29 to 1.49%	2.93 to 3.50%	-4.94 to 4.00%	
Threohydrobupropion	5 to 2500 ng/mL (20X)	1.72 to 2.90%	-0.14 to 5.85%	2.48 to 4.20%	-2.67 to 3.75%	
Erythrohydrobupropion	1 to 500 ng/mL (20X)	1.66 to 7.45%	-0.49 to 8.08%	2.72 to 5.01%	-2.52 to 2.29%	
Lisinopril	0.50 to 250.50 ng/mL (2535 ng/mL; 20X)	0.63 to 10.93%	-5.56 to 0.58%	2.66 to 10.92%	-2.12 to 0.02%	(b) (4) Project Number 65129 partial validation 2
Glyburide	2.00 to 400 ng/mL (3,000 ng/mL;10 X)	1.9 to 5.6%	-8.5 to 15.2%	4.6 to 6.0%	-2.0 to 12.2%	(b) (4) Project Number ZZ17229-01
Atorvastatin	0.300 to 50.0 ng/mL (200 ng/mL; 10X)	1.0 to 6.2%	-8.3 to 0.2%	0.0 to 3.5%	-4.8 to -0.8%	(b) (4) Report Number (b) (4) 08-367
para-Hydroxy Atorvastatin		1.2 to 7.9%	-2.6 to 3.4%	0.0 to 3.7%	-1.2 to -0.4%	
ortho-Hydroxy Atorvastatin		0.9 to 5.5%	-7.9 to 0.0%	0.9 to 4.1%	-3.0 to -1.8%	
Valsartan	50.0 to 10,000 ng/mL (20,000 ng/mL; 10X)	2.0 to 6.4%	-6.5 to 2.0%	0.0 to 2.8%	-3.6 to -0.2%	(b) (4) Report Number (b) (4) 07-115
Nifedipine	1.00 to 250 ng/mL (1,000 ng/mL; 10X)	0.7 to 3.4%	-4.5 to 8.0%	3.1 to 4.5%	1.0 to 5.0%	(b) (4) Report Number (b) (4) 08-274
Metoprolol	0.500 to 250 ng/mL (1250 ng/mL; 10X)	0.6% to 15.7%	-8.4% to 9.3%	0.0% to 5.9%	-3.4% to 4.7%	(b) (4) Report Number (b) (4) 06-115

Abbreviations: CV = coefficients of variation, DF= dilution factor, QC = quality control

3 Labeling Comments (Preliminary Major Recommendations)

Note: Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Proposed Text:
Under Section "5.2 Seizures"
Add the following item to the "Recommendations for Reducing the Risk of Seizure:"
Contrave should not be taken with high-fat meal.

Under Section 8 "USE IN SPECIFIC POPULATIONS"
8.5 Geriatric Use
Clinical studies of CONTRAVE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Older individuals may be more sensitive to the central nervous system adverse effects of CONTRAVE. Naltrexone and bupropion are known to be substantially excreted by the kidney, and the risk of adverse reactions to (b) (4) 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~~ Contrave should be used with caution in elderly patients. Contrave results in slight increase in serum creatinine, therefore renal function should be monitored. ~~it may be useful to monitor renal function.~~

8.7 Renal Impairment

(b) (4) . (b) (4)

Under "Section 12 Clinical Pharmacology" add the following text under Renal Impairment:

(b) (4)

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

PREFACE: CONTRAVE is a combination drug product containing Naltrexone and Bupropion in a single tri-layer tablet formulation. Wherever applicable, dose strengths for Naltrexone (N) and Bupropion (B) components (indicated as NB in the text of this review) in mg are indicated as total daily dose of each component administered e.g. NB 16/360 or NB 32/360.

1 SUMMARY OF FINDINGS

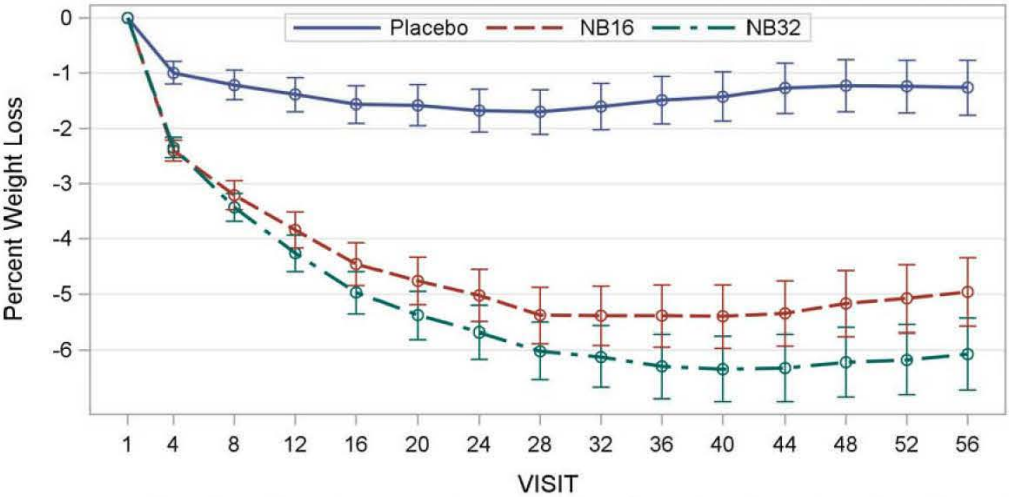
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 What is the dose-response relationship for weight loss in obese patients?

The percent weight loss versus time profile from Phase 3 trial NB-301 shows that the maximal mean percent reduction in weight from baseline is achieved after week 28 in both low (NB 16/360) and high dose (NB 32/360) treatment arms (*Figure 1*). These two treatment arms differed in the total daily naltrexone dose; 16 mg versus 32 mg, while receiving same total daily dose of 360 mg Bupropion.

Figure 1. Time course of percent weight loss from baseline in the 56-week Phase 3 confirmatory trial (NB-301)



Placebo	511	507	510	511	511	511	511	511	511	511	511	511	511	511	511
NB16	471	467	471	471	471	471	471	471	471	471	471	471	471	471	471
NB32	471	467	471	471	471	471	471	471	471	471	471	471	471	471	471

The dose-weight loss relationship at week 56 shows that Contrave treatment is associated with a dose dependent reduction in weight from baseline (*Figure 2*). However, the weight loss with Contrave treatment was marginal as the maximal placebo adjusted weight loss was 4.8%, achieved with the NB 32/360 mg dose. This efficacy result does not satisfy one of the two efficacy benchmarks recommended in the FDA Guidance document on "Developing Products for Weight Management". According to the Guidance "*In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:*

• *The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*

• *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant".*

NB 32/360 mg dose also shows a numerical advantage over NB 16/360 mg dose with regards to maximal weight loss (See *Table 1* below).

Figure 2. Dose dependent increase in effectiveness of Contrave based on Mean(±SE) % Weight Loss from baseline at week 56 (Phase 3 trial NB-301)

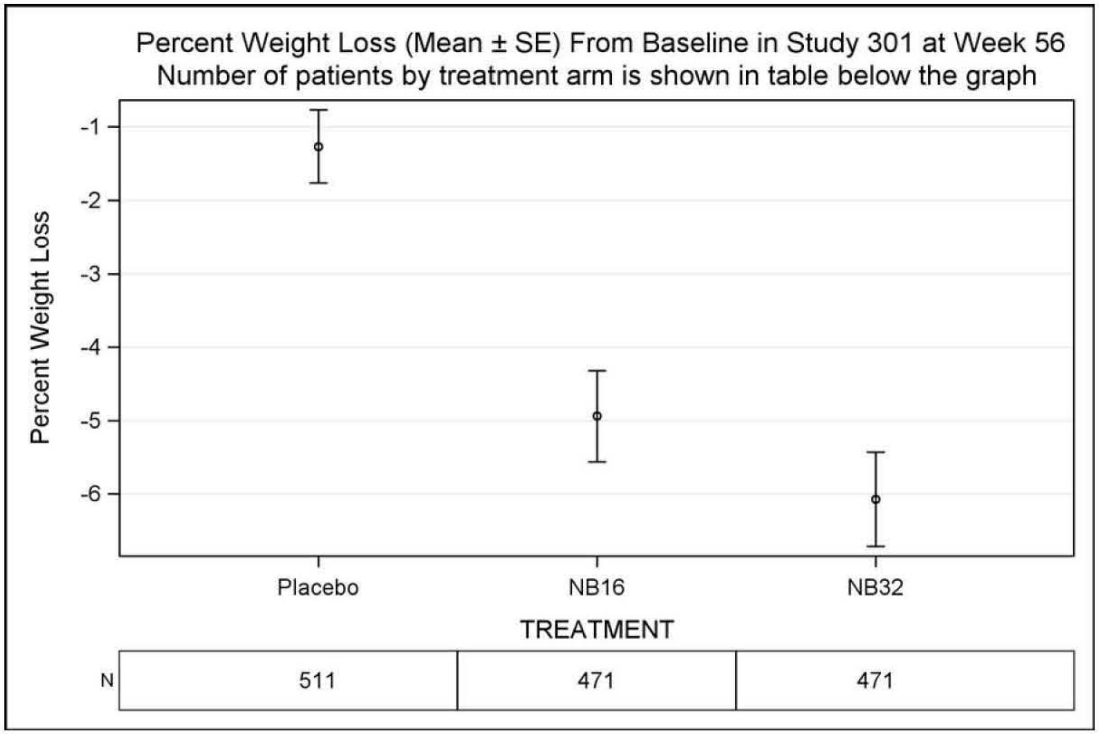


Table 1. Body Weight (kg), Percent Change from Baseline to Endpoint in Trial NB-301 (Full Analysis Set)

Statistic	Placebo (n=511)	NB16 (n=471)	NB32 (n=471)
Baseline mean (SD)	99.29 (14.33)	100.11 (14.41)	100.17 (16.26)
% change from baseline, LSMean (SE)	-1.33 (0.30)	-5.00 (0.31)	-6.14 (0.31)
LSMean difference from placebo (SE)	--	-3.67 (0.42)	-4.81 (0.42)
95% CI	--	(-4.50, -2.85)	(-5.63, -3.99)
p-value	--	< 0.001	< 0.001
LSMean difference from NB16	--	--	-1.14
95% CI	--	--	(-1.98, -0.30)
p-value	--	--	0.008

Abbreviations: NB16=Naltrexone SR 16 mg/Bupropion SR 360 mg, NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg, CI=Confidence Interval

(Reference: Table 2.7.3-2 Section 2.7.3 Summary of Clinical Efficacy Page 13)

Numerical benefit of NB 32/360 mg dose was also evident from a greater percentage of subjects loosing >5% weight with this dose against NB16/360 mg and placebo (see *Table 2* below). Thus, this efficacy result met second efficacy benchmark recommended by the Guidance for both NB16 and NB32 doses from Trial NB-301.

Table 2. Proportion of patients achieving ≥5% Weight Loss at Endpoint by Treatment in Trial NB-301 (Full Analysis Set)

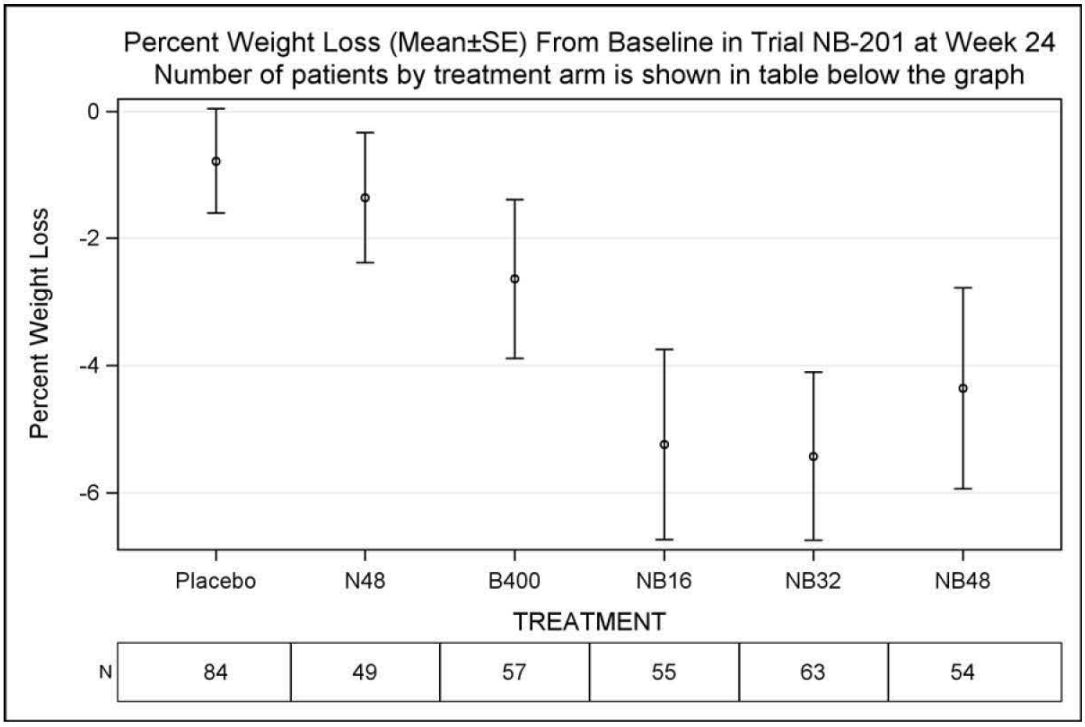
Statistic	Placebo (n=511)	NB16 (n=471)	NB32 (n=471)
No. (%) with ≥ 5% decrease	84 (16.44%)	186 (39.49%)	226 (47.98%)
95% CI	(13.22%, 19.65%)	(35.08%, 43.91%)	(43.47%, 52.49%)
Odds ratio vs. placebo	--	3.42	4.86
95% confidence limit for odds ratio	--	(2.52, 4.63)	(3.60, 6.57)
p-value	--	< 0.001	< 0.001
Odds ratio vs. NB16	--	--	1.42
95% confidence limit for odds ratio	--	--	(1.09, 1.85)
p-value	--	--	0.010

Abbreviations: NB16=Naltrexone SR 16 mg/Bupropion SR 360 mg, NB32=Naltrexone SR 32 mg/Bupropion SR 360 mg, CI=Confidence Interval

(Reference: Table 2.7.3-3 Section 2.7.3 Summary of Clinical Efficacy Page 14)

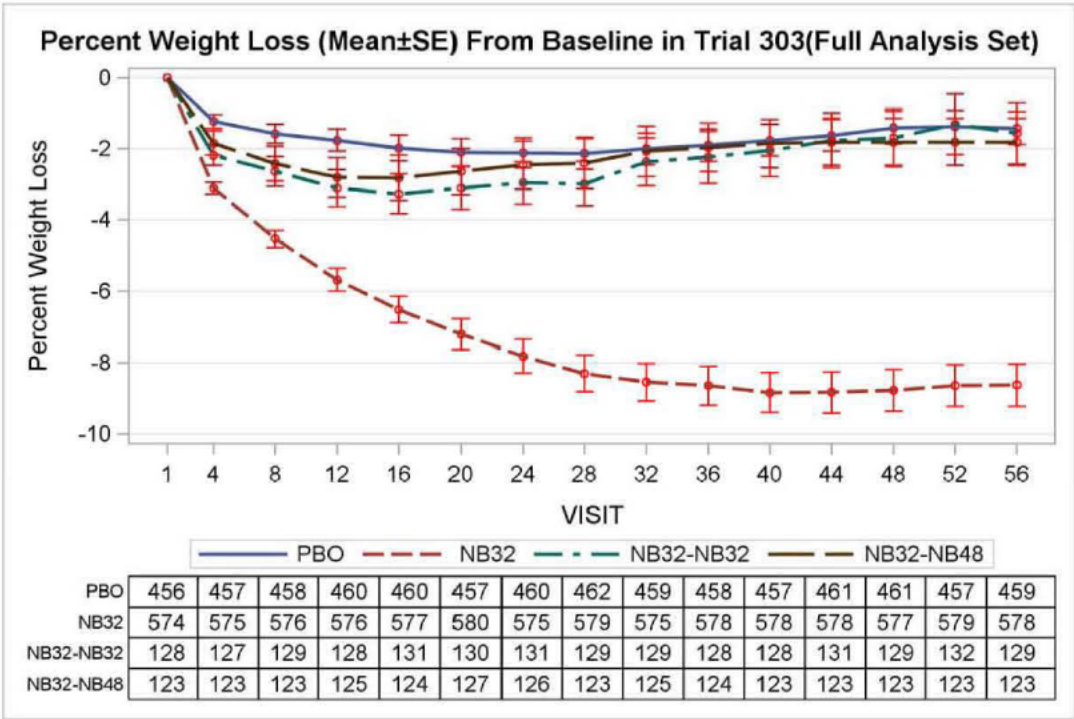
Dose-response data from Phase 2 trial also demonstrated that co-administration of Naltrexone (16 or 32 mg total daily dose) and Bupropion (400 mg total daily dose) results in additive increase in weight loss over the monotherapy with Naltrexone (48 mg total daily dose) or Bupropion (400 mg total daily dose). However, the NB48 treatment did not show any benefit over the NB16 or NB32 treatments and the B400 (Bupropion 400 mg monotherapy treatment (see *Figure 3*).

Figure 3. Co-administration of Naltrexone and Bupropion results in additive weight loss versus monotherapy based on Mean(±SE) % Weight Loss from baseline at week 24 (Phase 2 trial NB-201)



Phase 3 Trial NB-303 also tested the dose escalation to NB48 (Naltrexone 48 mg and Bupropion 360 mg total daily dose) for subjects who did not loose >5% weight by Week 28. The percent weight loss versus time by treatment arms in Trial NB-303 is presented in *Figure 4* below. The escalation of dose to NB48 did not show any benefit with regards to improvement in weight loss.

Figure 4. Time course of percent weight loss from baseline by pooled treatment arms in the 56-week Phase 3 confirmatory trial (NB-303)



PBO	456	457	458	460	460	457	460	462	459	458	457	461	461	457	459
NB32	574	575	576	576	577	580	575	579	575	578	578	578	577	579	578
NB32-NB32	128	127	129	128	131	130	131	129	129	128	128	131	129	132	129
NB32-NB48	123	123	123	125	124	127	126	123	125	124	123	123	123	123	123

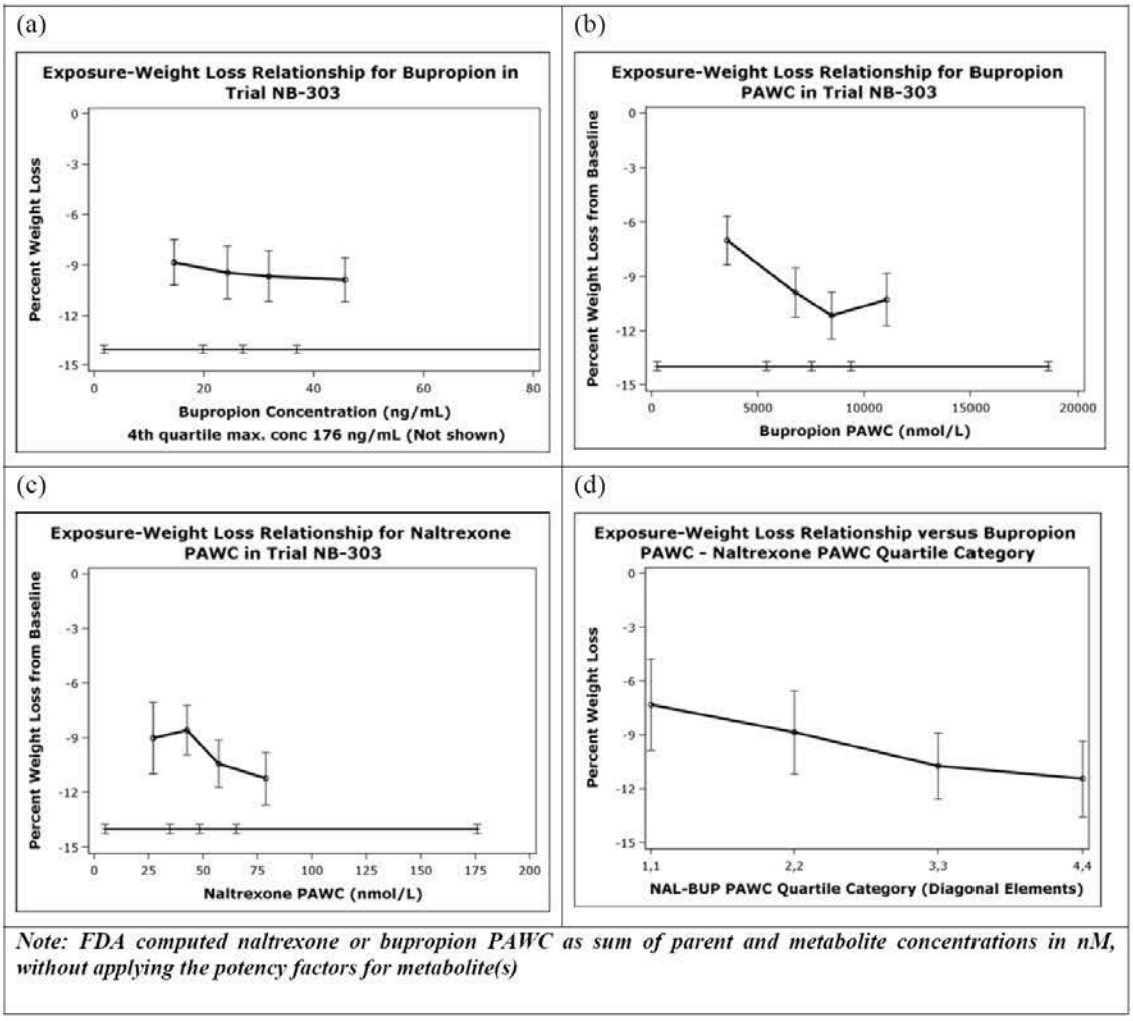
PBO: Placebo subjects, NB32: Subjects on active treatment who lost 5% or greater weight by week 28, NB32-NB32: Subjects loosing less than 5% weight and re-randomized to receive NB32, NB32-NB48: Subjects loosing less than 5% weight and re-randomized to receive NB48.

1.1.2 What is the systemic exposure-response relationship for weight loss in obese patients?

There was a shallow trend of increase in weight loss with increase in bupropion exposure. Similar trend was observed with increasing bupropion PAWC, naltrexone PAWC. The systemic exposure for Bupropion, Naltrexone and their respective major metabolites was collected in 395 active treatment subjects (42% including placebo, 30% on NB32 treatment), a subset of Trial NB-303 population. Mean±SE weight loss was plotted against the median of each of the four quartiles for bupropion concentration. The 3 major metabolites of bupropion namely hydroxybupropion, erythrohydrobupropion and threohydrobupropion are considered to be pharmacologically active (antidepressant screening test in mice). Similarly, 6-beta naltrexol, the major metabolite of Naltrexone is also considered pharmacologically active. A composite metric, abbreviated as PAWC (Pharmacological Activity Weighted Composite) was computed by the sponsor for these analytes by converting the concentrations to nanomoles (nM) and assuming a potency factor of 0.6 for hydroxybupropion, 0.2 for erythrohydrobupropion and threohydrobupropion relative to parent bupropion, and 0.2 for 6-beta naltrexol relative to Naltrexone. However, these potency factors are based on animal data and their relevance in weight loss effect in humans is unknown. Therefore, we consider the exposure-response analysis based PAWC metric as exploratory. For FDA's exploratory exposure-

response PAWC was computed as sum of parent and metabolite concentrations in nM, without applying the potency factors for metabolites. Percent weight loss (Mean±SE) was plotted against the median of each of the four quartiles for bupropion PAWC concentration (see *Figure 10*).

Figure 5. Systemic Exposure-Response from the 56-week Phase 3 confirmatory trial (NB-303)



Note: FDA computed naltrexone or bupropion PAWC as sum of parent and metabolite concentrations in nM, without applying the potency factors for metabolite(s)

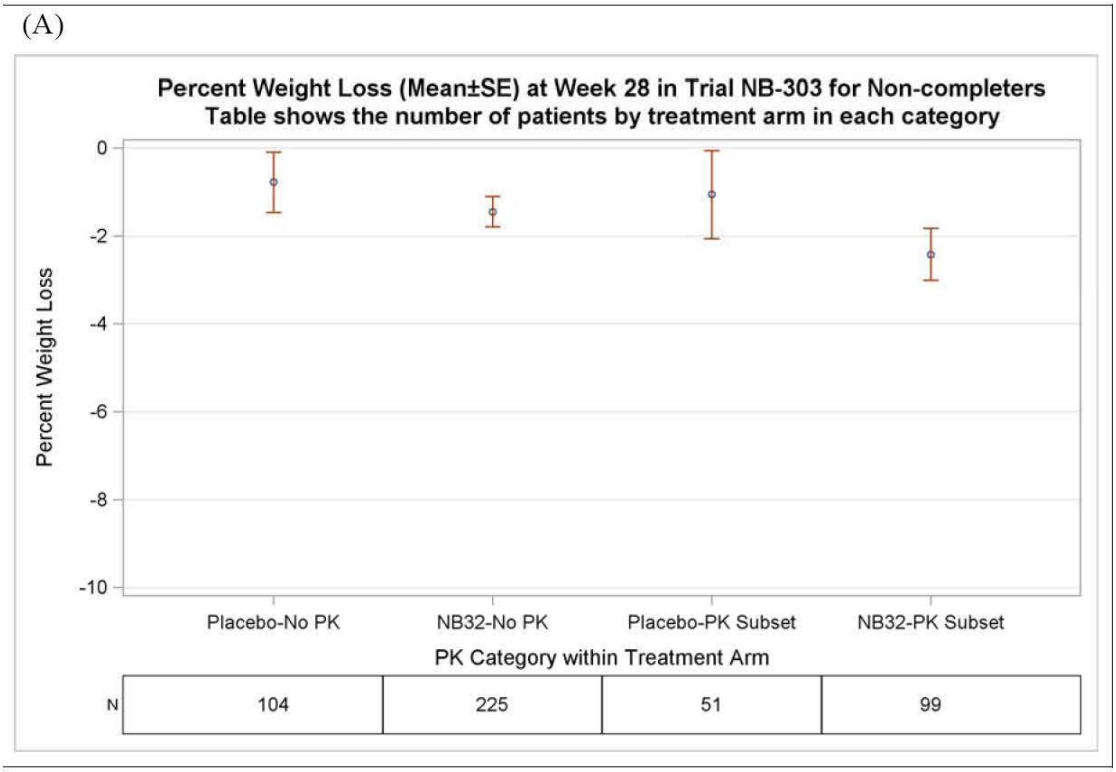
Exposure-weight loss relationship versus bupropion concentrations shows a flat response surface (*Figure 10a*) indicating that the observed bupropion concentrations were associated with the maximum attainable weight-loss response. Though there was an exposure-response relationship evident from weight loss versus bupropion PAWC plot, indicating that metabolites may have a role in overall weight-loss effect of bupropion (*Figure 10b*). Since this is combination therapy, the exposure-response evaluation needs

to consider contribution from both the components to the overall response. Therefore, percent weight loss was plotted across the quartile categories, which represented the diagonal elements of the 4 x 4 matrix formed by four quartiles each of Bupropion and Naltrexone PAWC concentrations. A shallow relationship was evident from the graph (*Figure 10c*) that shows increase in weigh-loss effect as concentrations simultaneously move up into the higher quartiles of Naltrexone and Bupropion PAWC, indicating a weaker but possible synergistic effect.

Noticeably, the range of percent weight loss seen in the exposure-response plots was greater in than that shown in the dose-response plots. This could be explained by the fact that the PK data was collected in a subset of the trial population. There were more completers (*Table 3*) in PK-"Yes" category likely due to their "responder" nature, which is reflected by the greater extent of mean weight loss seen at week 28 in PK-"Yes" versus PK-"No" category (*Figure 6*). This suggests that this subset is not representative of the whole population from an exposure-response for efficacy perspective.

Figure 6. Among Week 28 Non-completers (A) and Completers (B) Mean percent weight loss at week 28 was greater in subjects with PK sampling than subjects in whom PK data was not collected (Phase 3 Trial NB-303)

(A)



(B)

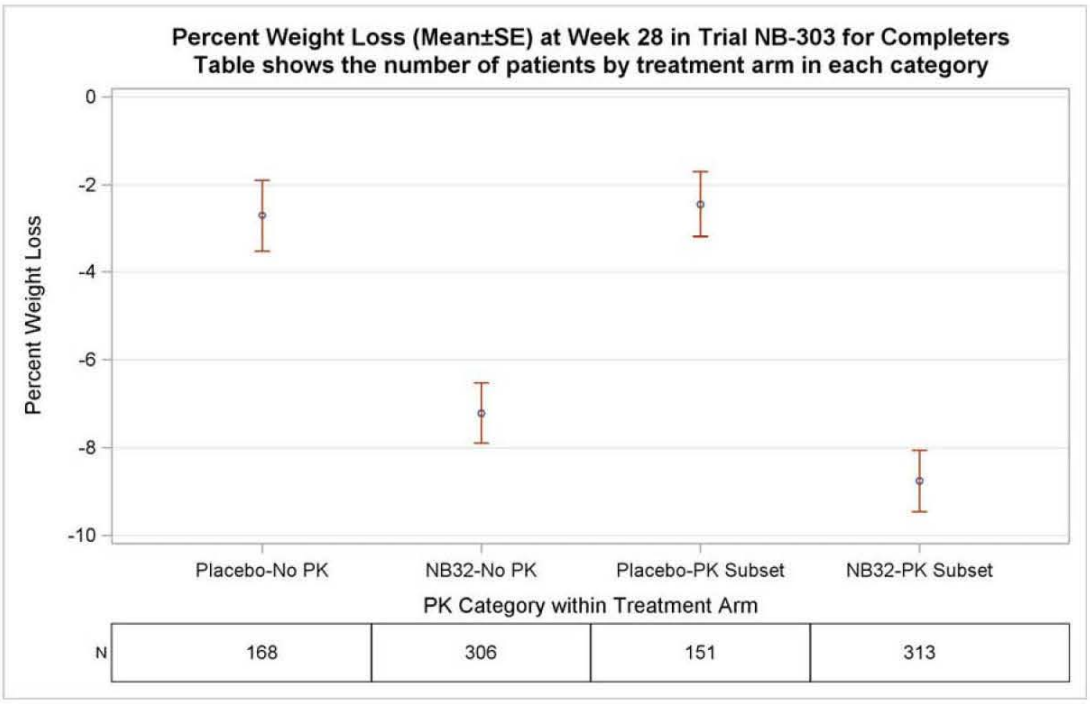


Table 3. Percent Weight loss from Baseline at Week 28 Endpoint in Trial NB-303 among subjects with and without PK sampling

Week 28 Non-Completers							Week 28 Completers						
	TREATMENT							TREATMENT					
	NB32			PLACEBO				NB32			PLACEBO		
PK	Percent Change from Baseline			Percent Change from Baseline			PK	Percent Change from Baseline			Percent Change from Baseline		
	N (%)	Mean	SE	N (%)	Mean	SE		N (%)	Mean	SE	N (%)	Mean	SE
No	225 (43)	-1.45	0.17	104 (38)	-0.78	0.34	No	306 (57)	-7.22	0.35	168 (68)	-2.71	0.41
Yes	99 (24)	-2.42	0.30	51 (25)	-1.06	0.50	Yes	313 (76)	-8.76	0.36	151 (75)	-2.45	0.38

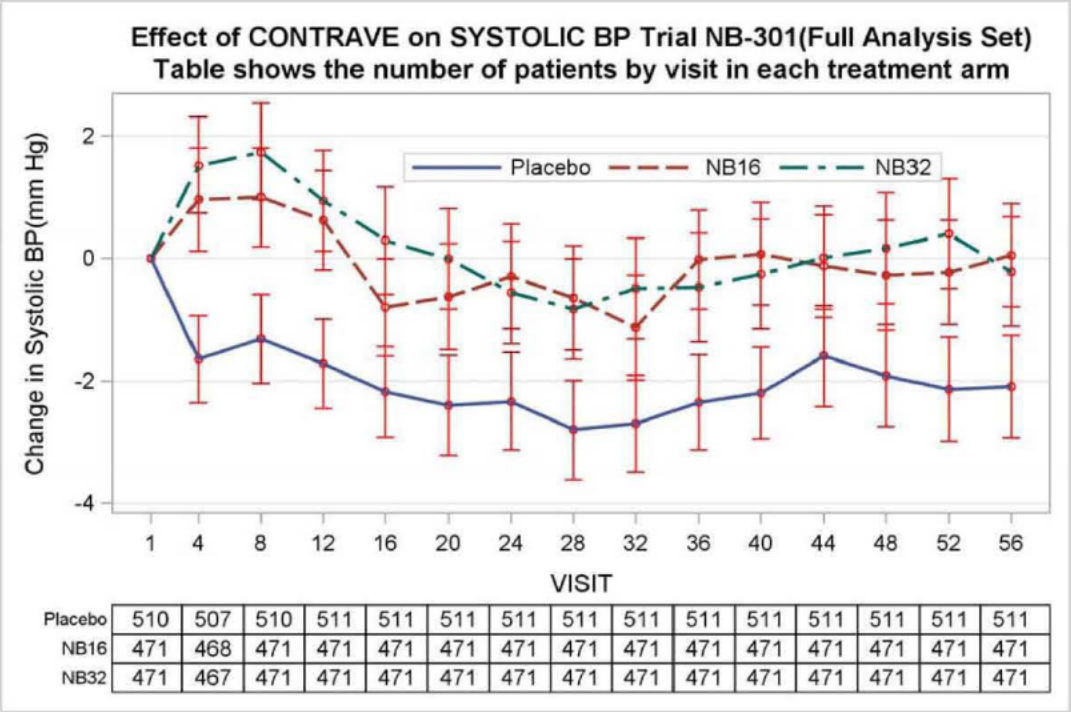
Note: (%) based on comparison by row between Week 28 completer and non-completer status in each treatment arm.

1.1.3 What is the exposure-response relationship for Contrave with regards to blood pressure, gastro-intestinal, and psychiatric effects in obese patients?

Effects of Contrave Treatment on Blood Pressure:

Bupropion is known to increase the blood pressure through unknown mechanism. Contrave treatment was also associated with an increase in systolic blood pressure (SBP) in obese patients. Data from placebo controlled Trial NB-301, which tested two dose levels of the combination (bupropion dose was same 360 mg/day), showed that the maximum mean increase of around 1 to 2 mm Hg from baseline was observed up to Visit 8 with the active treatment arms (*Figure 7*). This mean rise in systolic BP returned to baseline by week 16. The placebo group showed greater reduction in BP from baseline.

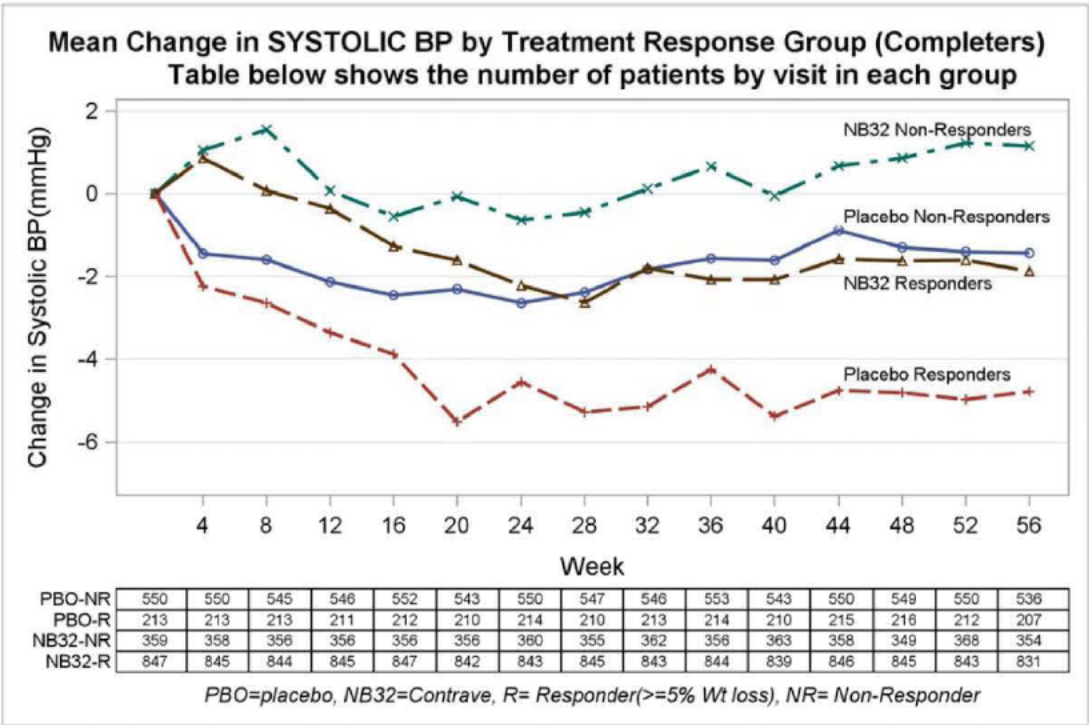
Figure 7. Mean (SE) systolic blood pressure change from baseline in the 56-week Phase 3 confirmatory trial (NB-301).)



Placebo	510	507	510	511	511	511	511	511	511	511	511	511	511	511	511
NB16	471	468	471	471	471	471	471	471	471	471	471	471	471	471	471
NB32	471	467	471	471	471	471	471	471	471	471	471	471	471	471	471

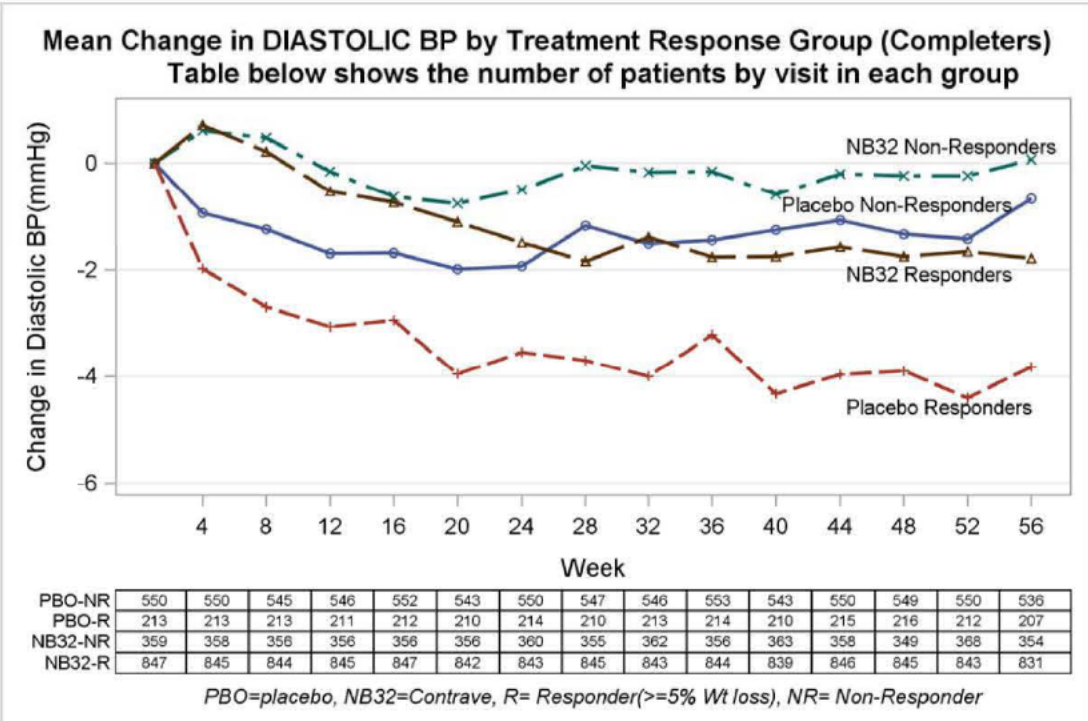
Pooled data from placebo controlled trials NB-301, NB-302, NB-303 and NB-304 showed that the maximum mean increase of around 1 to 2 mm Hg from baseline was observed around Week 4 to 8 in the active treatment arms. This mean rise in systolic BP returned to baseline by week 16 for the active treatment group. However, the change from baseline profile differed based on the response status. The responders in placebo and active treatment group showed greater reduction in BP from baseline. Similar trends were observed for Diastolic Blood Pressure and Pulse Rate (see *Figure 8*). Therefore, overall the beneficial effect of weight loss in terms of reduction in BP was absent in the Contrave treatment group.

Figure 8. Change in Systolic Blood Pressure from baseline (Mean±SE) versus Time (weeks) by Treatment in Phase 3 confirmatory trials (pooled data from NB-301, NB-302, NB-303, NB-304; Completers)



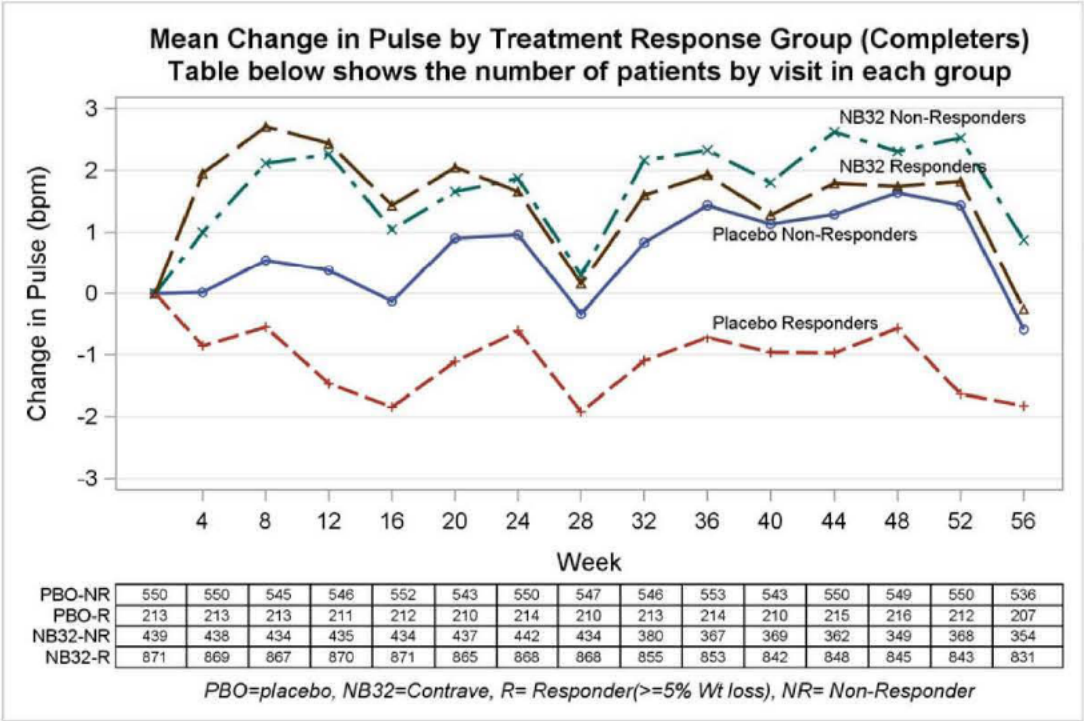
PBO-NR	550	550	545	546	552	543	550	547	546	553	543	550	549	550	536
PBO-R	213	213	213	211	212	210	214	210	213	214	210	215	216	212	207
NB32-NR	359	358	356	356	356	356	360	355	362	356	363	358	349	368	354
NB32-R	847	845	844	845	847	842	843	845	843	844	839	846	845	843	831

PBO=placebo, NB32=Contrave, R= Responder(>=5% Wt loss), NR= Non-Responder



PBO-NR	550	550	545	546	552	543	550	547	546	553	543	550	549	550	536
PBO-R	213	213	213	211	212	210	214	210	213	214	210	215	216	212	207
NB32-NR	359	358	356	356	356	356	360	355	362	356	363	358	349	368	354
NB32-R	847	845	844	845	847	842	843	845	843	844	839	846	845	843	831

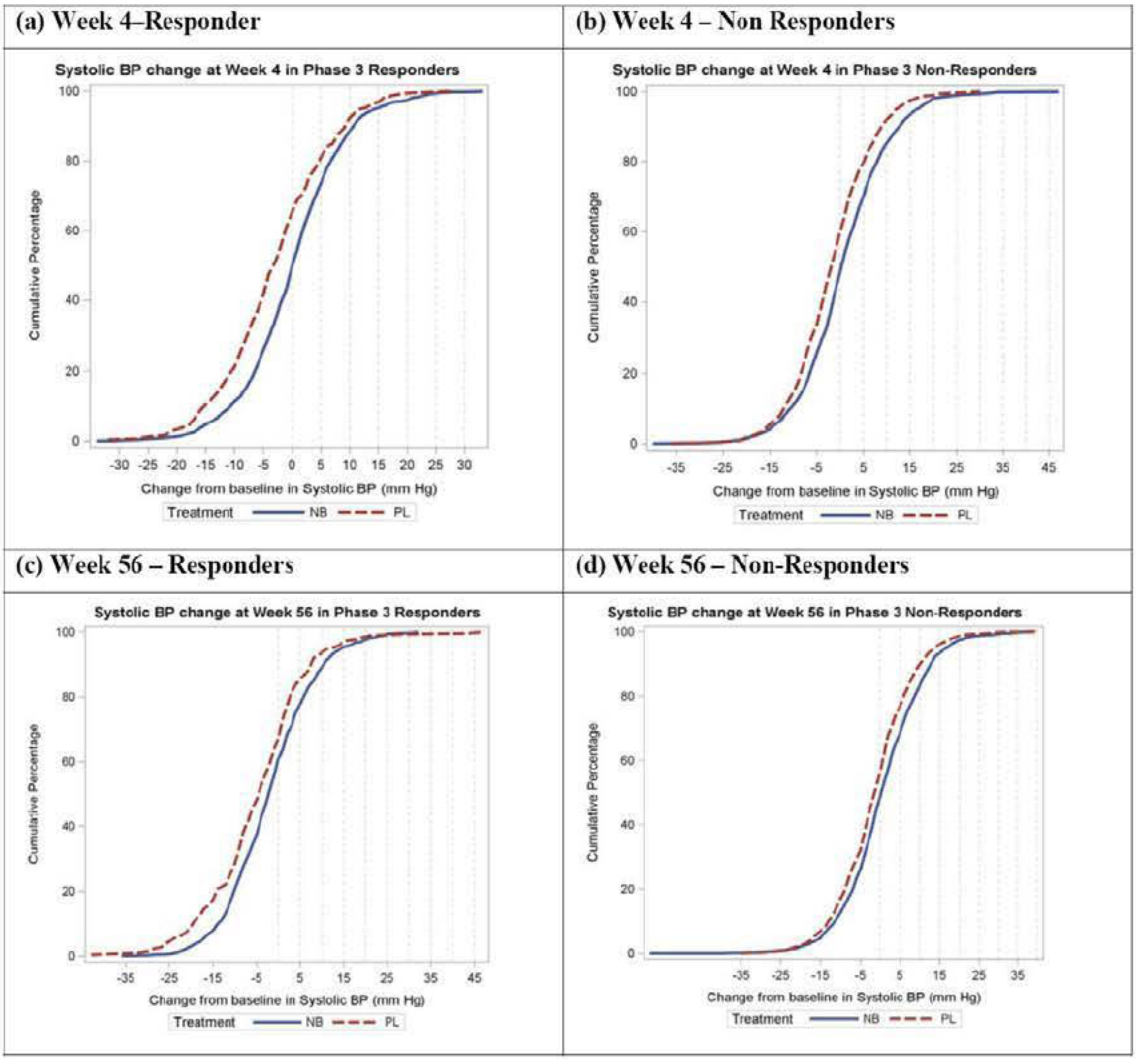
PBO=placebo, NB32=Contrave, R= Responder(>=5% Wt loss), NR= Non-Responder



To determine the risk to patients with respect to the maximum BP increase, cumulative percentage of subjects were plotted versus the change in BP for the pooled Phase 3 data for active (NB32) versus the placebo treatments, both at week 4 and 56, stratifying by responder/non-responder status (subjects who lost 5% or more weight from baseline at week 56). The plots clearly showed a distinction between the placebo and active treatment arms regardless of the response group (shift to the right) (*Figure 9*).

Based on the cumulative frequency distribution top 5% of responder patients in the Contrave treatment arm had ~2 mm Hg increase from baseline over the top 5% placebo responders at Week 4. At week 56, this difference was ~3 mm Hg in top 5% patients among responders. Among the non-responder population, this difference against placebo was ~5 and 3 mm Hg at Week 4 and 56, respectively.

Figure 9. Cumulative Percentage of Subjects versus Systolic BP Change from Baseline by Treatment in Pooled Data from Phase 3 confirmatory trials



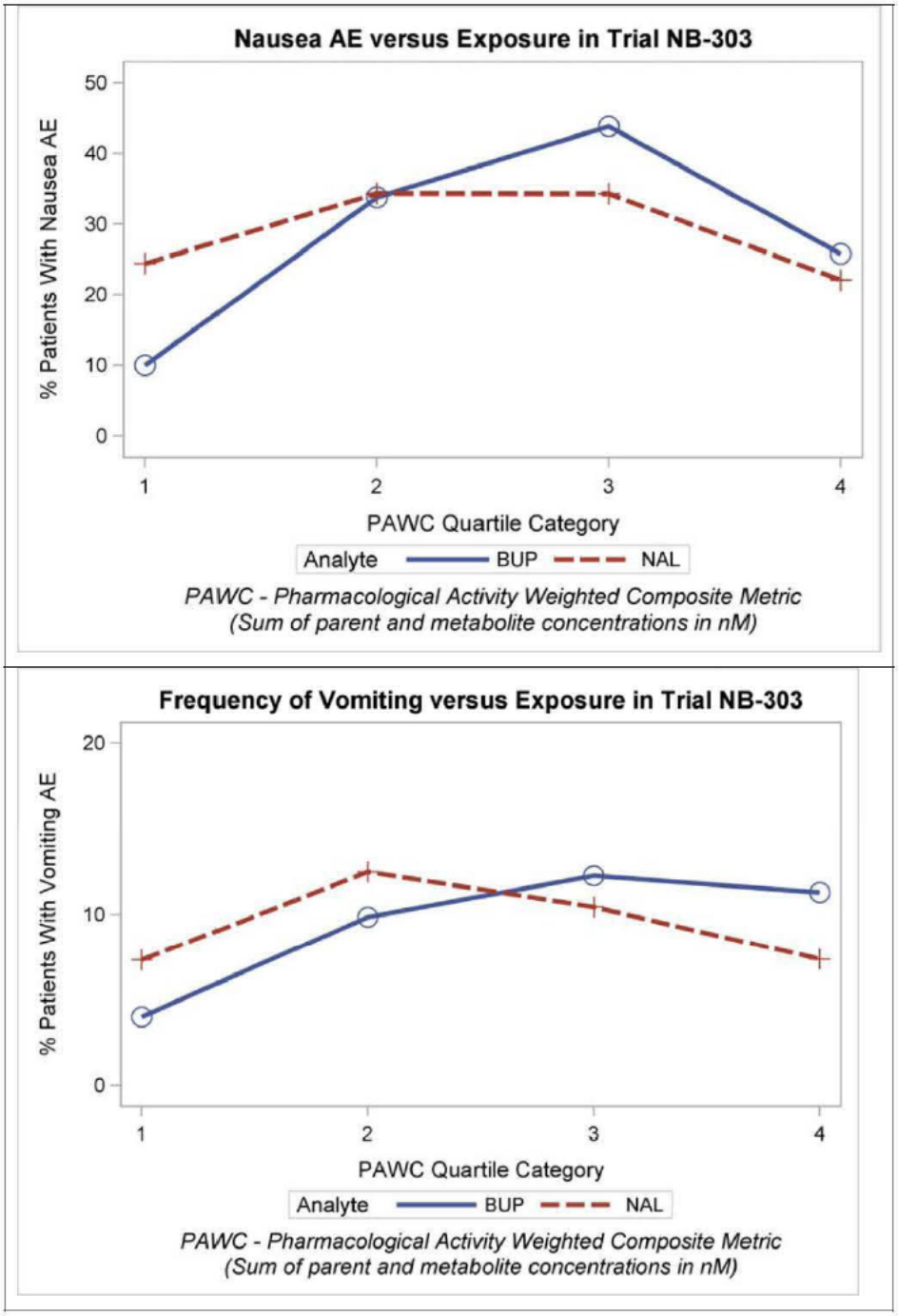
Exposure-systolic BP mean change from baseline in Trial NB-303 analysis, however, did not show any trend for BP change with increasing bupropion exposure. This is more likely due to the fact that PK subset happen to be the patients who lost more weight than those in whom PK data was not collected

Treatment Emergent Gastro-intestinal and Psychiatric Adverse Events (TEAEs):

The percentage of subjects with vomiting and to some extent nausea increased with increase in the bupropion PAWC metric (*Fig. 10a*) across four quartiles. No such

relationship was apparent with increase in naltrexone PAWC metric across four quartiles. Percentage of subjects with insomnia and anxiety did not show increase with either bupropion PAWC or naltrexone PAWC metrics.

Figure 10. Exposure-Response for Treatment Emergent Adverse Events of Nausea and Vomiting in 56-week Phase 3 confirmatory trial (NB-303)

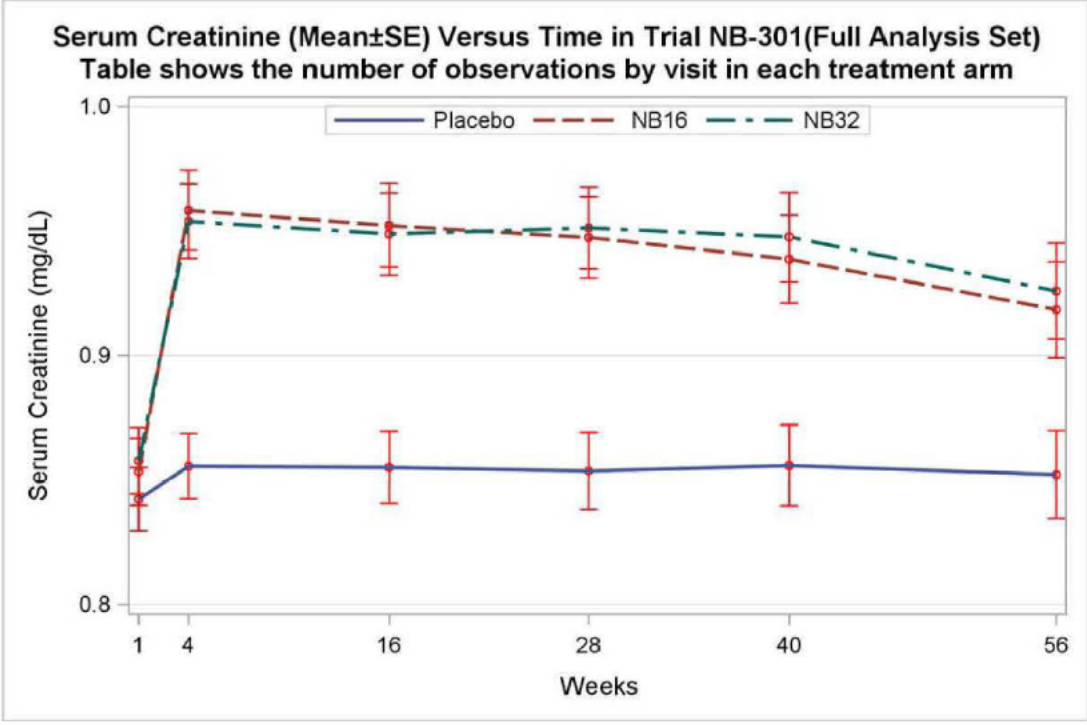


Further, there were no differences seen in the distribution of exposure of bupropion, naltrexone and respective PAWCs among the subjects with and without psychiatric and gastrointestinal adverse reactions (see Appendix 1 for details).

Effects on Serum Creatinine:

The clinical trial data showed increase in serum creatinine from baseline in the Contrave treated patients. A representative graph from one of the Phase 3 trial NB-301 is shown in *Figure 11* below.

Figure 11. Serum creatinine versus time by treatment in Trial NB-301



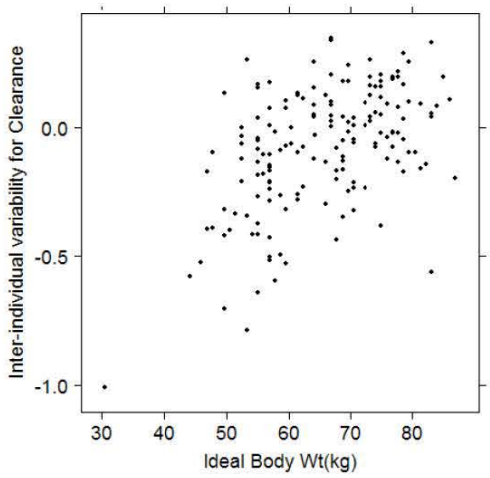
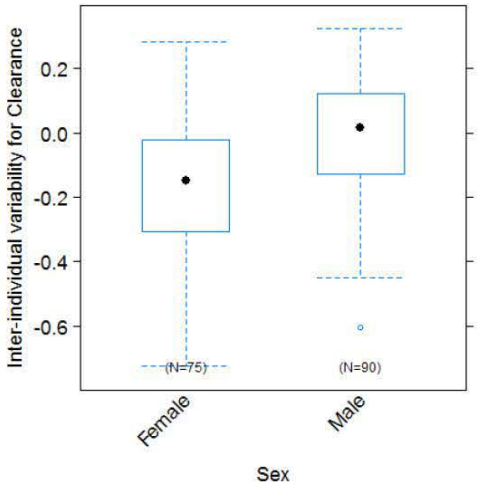
This was in part explained based on the in vitro transporter inhibition study results, which demonstrated that bupropion and its metabolites, specifically threohydrobupropion and erythrohydrobupropion inhibit Organic Cation Transporter (OCT2) with Cmax, free/IC50=0.29 (Ratio>0.1 is considered clinically relevant). OCT2 is involved in tubular secretion of creatinine and other drugs e.g. metformin, and serum creatinine increase has been observed with other drugs known to interact with OCT2 such as cimetidine. Thus, slight increase in serum creatinine noted in the Phase 3 trials could be due to OCT2 inhibition.

1.1.4 What is the influence of body weight, gender and race on PK of Contrave in obese patients?

The major metabolite of bupropion is hydroxybupropion and naltrexone is metabolized to one major metabolite 6-beta naltrexol. Though sponsor modeled each of the 6 analytes (bupropion + 3 metabolites, and naltraxone + 1 metabolite) separately, only parent and their major metabolites are evaluated to answer this question.

Bupropion: Ideal body weight was found to influence the apparent clearance of bupropion, as shown in *Figure 12a*. However, the relationship between ideal body weight and clearance was shallow (Exponent 0.43) and it only explained 5% points of inter-individual variability (IIV) in CL/F. The apparent volume of distribution Vc/F increased with increasing ideal body weight (Exponent 1.12), and ideal body weight explained 10% points of IIV in Vc/F.

Figure 12. Bupropion clearance increases with increase in ideal body weight

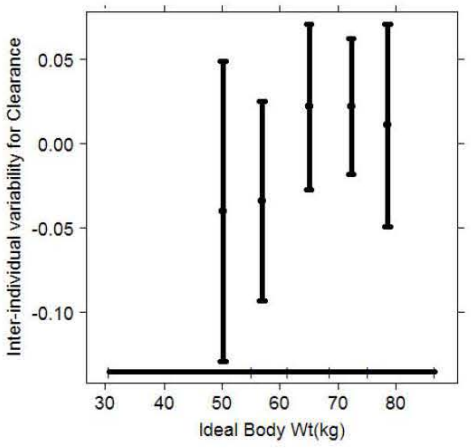
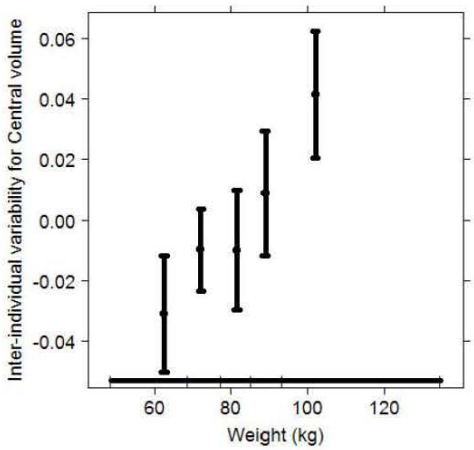
(a) Inter-individual variability in bupropion clearance versus Ideal Body Weight from base model	(b) IBW adjusted Clearance versus Gender
	

According to the sponsor's analysis, bupropion F was higher in women when compared with men, with an estimate of 1.20 (1.08, 1.37) relative to men. There was an almost 50% probability of bupropion bioavailability for females being greater than 125% of the typical male, suggesting that sex may have an influence on bupropion first-pass metabolism. The ideal body weight adjusted clearance on average showed difference among males and females (*Figure 12b*).

The effect of age or race (Whites versus Non-whites) on bupropion clearance was not evident from the data.

Hydroxybupropion: Hydroxybupropion Vc/F increased with increasing IBW and WT, respectively. Ideal body weight, age and race had no effect on hydroxybupropion CL/F.

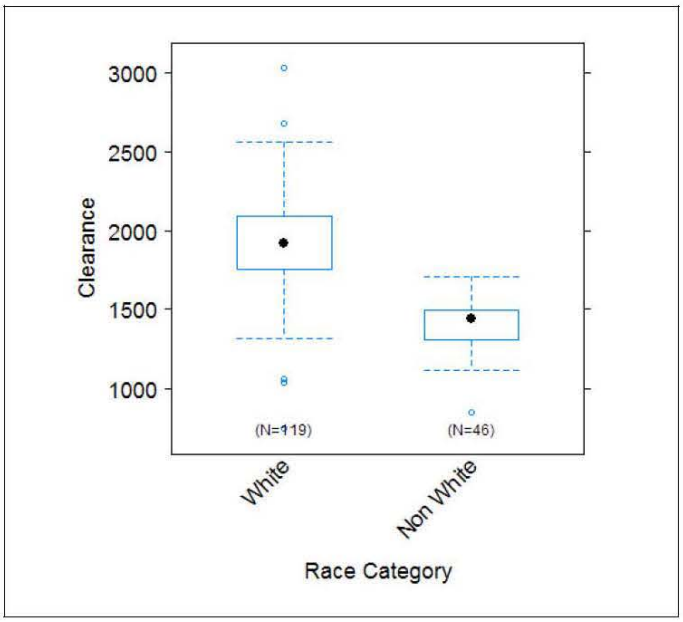
Figure 13. Hydroxybupropion clearance and volume of distribution increases with increase in ideal body weight and total body weight, respectively

(a) Inter-individual variability in hydroxybupropion clearance versus Ideal Body Weight from base model	(b) Inter-individual variability in hydroxybupropion volume of distribution versus total body weight from base model
	

Naltrexone:

Naltrexone CL/F in non-whites was 34% lower than white subjects. Effect of other covariates such as ideal body weight, weight, age and sex on the naltrexone PK could not be established as the estimates lacked precision.

Figure 14. Naltrexone apparent clearance was lower in non-white patients



6-Beta Naltrexol:

6-beta-natrexol Vc/F increased with increasing weight. Effect of age, race, and ideal body weight on CL/F was poorly defined and not estimated with sufficient precision to make definitive statements concerning this covariate effect.

1.1.5 Do any of the covariates warrant for Contrave dose adjustment?

No, based on the results of the population PK analysis, no dose adjustment is necessary based on ideal body weight, weight, age, gender, or race. These covariates do not affect the Contrave pharmacokinetics in a clinically meaningful way.

1.1.6 Do any of the safety findings warrant for Contrave dose adjustment?

The exposure-safety analysis did not indicate any safety concern warranting for dose adjustments from a Pharmacometrics perspective. Since only one dose of bupropion was evaluated in the Phase 3 trials, there was no dose-response analysis possible for effect of bupropion on blood pressure. Therefore, comparison with placebo was done. Notably, the dose-efficacy relationship for Contrave reveals that there is no window of bupropion dose adjustment as the efficacy at doses below a total daily dose of 360 mg bupropion and 32 mg total daily dose of naltrexone is marginal.

1.1.7 Do the population PK analysis results support the sponsor's proposed labeling claims for Contrave in obese patient population?

Yes, sponsor's proposed labeling language, which specifies no dose adjustment based on ideal body weight, age, gender and race, is justified.

1.2 Recommendations

The sponsor's proposed doses are acceptable from clinical pharmacology perspective.

1.3 Label Statements

The proposed labeling statements for no dose adjustment for age, gender, and race are acceptable.

2 PERTINENT REGULATORY BACKGROUND

Orexigen Therapeutics (the sponsor) is seeking an approval of CONTRAVE® (naltrexone HCL and bupropion HCL, **NB**) Extended-Release Tablets for the treatment of obesity and weight management. The active pharmaceutical ingredients in NB drug product are naltrexone HCL, a potent μ (mu) opioids antagonist, and bupropion HCL, a dopamine (DA) and norepinephrine (NE) reuptake inhibitor. Bupropion and naltrexone are approved drug products that have been in use for different indications.

Each CONTRAVE tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and a more rapidly dissolving inert layer separating each drug. CONTRAVE will be available as two naltrexone dosage strength tablets:

- CONTRAVE 8/90, (naltrexone HCL 8 mg/bupropion HCL 90 mg) (b) (4) tablets

- CONTRAVE 4/90, (naltrexone HCL 4 mg/bupropion HCL 90 mg) (b) (4) tablets

The proposed recommended daily dose of NB is two 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion. NB dosing is escalated over a 3-week period until achieving the total daily maintenance dose of 32 mg naltrexone and 360 mg bupropion. Treatment initiation and escalation with NB 4/90 tablets may be considered. If well tolerated, patients using NB 4/90 tablets should switch to NB 8/90 tablets to have their daily dose increased to the recommended maintenance daily dose of 32 mg naltrexone and 360 mg bupropion (two NB 8/90 tablets twice daily) to maximize weight loss. However, patients initiated with NB 8/90 tablets that experience treatment intolerance during the escalation or early maintenance period can be switched to NB 4/90 tablets.

3 RESULTS OF SPONSOR'S ANALYSIS

Sponsor's population PK analyses were conducted using nonlinear mixed-effects modeling software (NONMEM) (Icon Development Solutions, Hanover, MD). Models were developed on a Mac workstation with Intel Core Duo processor, OSX operating system and the GNU Fortran Compiler, GCC-3.4.0 (Mac OS X version, also known as G77, GNU Project, http://www.GNU.org/) and a computer grid with multiple compute nodes. Each node runs the Mac OS X operating system and utilizes the GNU Fortran compiler, GCC-3.4.0. NMQual 6.4.1 was used to track all code patches/options and install NONMEM. The first-order conditional estimation (FOCE) was employed for all model runs.

Separate population PK models were developed for naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion.

A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for this population PK analysis. First, predefined covariate-parameter relationships were identified based on scientific interest and mechanistic plausibility, and a full model was constructed, with care to avoid correlation or collinearity in predictors. Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision. An external predictive check model evaluation step was performed to assess the performance of the final model and parameters.

A population PK data set was also constructed for a Contrave Phase 3 trial (NB-303). The models developed from the Phase 1 data were fit to the Phase 3 data set with fixed-effects and random-effects parameters fixed to the values obtained from the Phase 1 analysis.

According to the Sponsor's Analysis from Phase 1 Data:
Sponsor's population PK analysis used clinical study data from 11 Contrave Phase 1 studies (NB-228, NB-229, NB-230, NB-231, NB-232, NB-233, NB-234, NB-235, NB-237, NB-238, and NB-239), including concentration observations, dosing histories, event times, and covariate factors.
The study population consisted of 139 males and 109 females with ages ranging from 19 to 61 years, weights ranging from 48.6 to 135 kg, and BMI ranging from 18.6 to 40.0 kg/m^2 (Table 4). There was not a balanced distribution of races in this study population,

with the majority of subjects being white or African American (Table 5). The continuous covariates, weight,
BMI, and CRCL, were positively correlated with correlation coefficients of at least 0.465 (Table 4). Distributions of all continuous covariates were similar in both sexes, except that males exhibited a slightly greater median weight, IBW, AST, and ALT.

Table 4. Summary of Continuous Covariates and their correlation: Modeling Data Set

Covariate	N	Minimum	Maximum	Median	Mean	SD
Age (y)	165	19.0	61.0	33.0	34.8	11.50
Weight (kg)	165	48.6	135.0	81.6	81.9	16.20
Body Mass Index (kg/m^2)	165	18.6	40.0	27.0	27.7	4.93
Ideal Body Weight (kg)	165	30.6	86.8	66.8	65.5	10.50
Creatinine CL (mL/min)	165	65.4	254.0	127.0	129.0	31.80
AST (U/L)	165	12.0	39.0	19.0	20.1	5.62
ALT (U/L)	165	6.0	74.0	18.0	21.1	11.90

	Age	Weight	BMI	IBW	CRCL	AST	ALT
Age	1.000	0.151	0.220	−0.041	−0.332	0.048	0.061
Weight	0.151	1.000	0.815	0.465	0.576	0.066	0.303
BMI	0.220	0.815	1.000	−0.117	0.600	−0.060	0.185
IBW	−0.041	0.465	−0.117	1.000	0.052	0.216	0.239
CRCL	−0.332	0.576	0.600	0.052	1.000	−0.126	0.113
AST	0.048	0.066	−0.060	0.216	−0.126	1.000	0.737
ALT	0.061	0.303	0.185	0.239	0.113	0.737	1.000

Table 5. Summary of Categorical Covariates

	Gender		**Race**				
	Female	Male	White	AA	Asian	PI	Other
Number	109	139	180	58	14	5	1
Percentage	44	56	73	23	2	2	< 1

AA = African American, PI = Pacific Islander

Naltrexone:

- A two-compartment model with zero-order drug delivery to the depot compartment and subsequent first-order absorption was chosen as the naltrexone base structural model. This model was parameterized in terms of apparent clearance in L/hr (CL/F), apparent central volume of distribution in L (Vc/F), apparent peripheral volume of distribution in L (Vp/F), apparent inter-compartmental clearance in L/hr (Q/F), zero-order dose duration in hr (D1), and absorption rate constant (hr^{-1}) (Ka).
- Inter-individual random-effect distributions were modeled using exponential variance models for CL/F and Vc/F. Given the variable nature of naltrexone sustained release (SR) absorption within subjects, between-occasion random effects were included for D1 and Ka. Although F was not identifiable, this

parameter was fixed to a value of 1 and between-occasion random effects were also included to further account for within-subject variation in naltrexone absorption.

- The typical estimates (95% CI) of naltrexone PK model parameters for the reference covariate effects (white race, 70 kg ideal body weight (IBW), 35 years) were:
  - CL/F = 1910 (1610, 2130) L/hr
  - Vc/F = 9060 (6990, 11200) L,
  - Vp/F = 7770 (5420, 11100) L,
  - Q/F = 319 (269, 398) L/hr,
  - Ka = 1.02 (0.809, 1.35) hr^{-1}, and
  - D1 = 0.554 (0.448, 0.700) hr.
- Naltrexone CL/F was reduced by a factor of 0.656 (0.490, 0.874) in non-white subjects when compared to whites. Race differences are evident for naltrexone CL/F, with an approximate 75% probability that CL/F will have a greater than 20% reduction for a non-white subject. The remaining covariates studied (IBW on CL/F and Vc/F; age on CL/F) were poorly defined and not estimated with sufficient precision to make definitive statements concerning these covariate effects.

6-Beta Naltrexol:

- A two-compartment model with zero order drug delivery to the depot compartment and subsequent first-order absorption was chosen as the 6-beta-naltrexol structural model. Inter-individual random effects were incorporated for CL/F and Vc/F and between-occasion random effects were included for F, D1 and Ka. Residual random effects were described with a proportional error model.
- The typical estimates (95% CI) of PK model parameters for the reference covariate effects (white race, 70 kg IBW, 70 kg total body weight, 35 years) were:
  - CL/F = 58.6 (54.0, 64.4) L/hr,
  - Vc/F = 481 (140, 552) L,
  - Vp/F = 450 (391, 674) L,
  - Q/F = 59.9 (46.9, 83.0) L/hr,
  - Ka = 1.02 (0.291, 1.22) hr^{-1}, and
  - D1 = 0.435 (0.365, 0.560) hr.
- The 95% CI for the age effect and race effect on CL/F was not distinguishable from the null value, and the probability for subjects to fall outside the 80% to 125% reference range was minimal. Therefore, age and race are not likely to be clinically important covariates for 6-beta-naltrexol CL/F. The effect of IBW on CL/F was poorly defined and not estimated with sufficient precision to make definitive statements concerning this covariate effect. 6-beta-natrexol Vc/F increased with increasing weight, with typical patients at the extremes of the IBW distribution having a large probability of having a Vc/F value outside the 80% to 120% reference range.

Bupropion:

- A two-compartment model with zero-order drug delivery to the depot compartment and subsequent first-order absorption was chosen as the bupropion

model. Inter-individual random effects were incorporated for CL/F and Vc/F and between-occasion random effects were included for D1, Ka, and F.

- The typical estimates (95% CI) of PK model parameters for the reference covariate effects (white race, male, 70 kg IBW, 35 years) were:
  - CL/F = 170 (158, 204) L/hr,
  - Vc/F = 741 (651, 865) L,
  - Vp/F = 1323 (1250, 1524) L,
  - Q/F = 71.5 (67.8, 81.1) L/hr,
  - Ka = 0.891 (0.769, 1.07) hr^{-1}, and
  - D1 = 0.433 (0.395, 0.468) hr.
- Bupropion CL/F and Vc/F increased with increasing IBW. Exponent estimates of 0.809 (0.489, 1.25) and 1.37 (0.926, 1.81) were similar to theoretical values for allometric exponents of 0.75 for CL/F and 1.0 for Vc/F. Patients with an IBW value at the extremes of the range had high probabilities of having CL/F and Vc/F values that were outside of the 80% to 125% reference range, suggesting that IBW may be an important covariate for bupropion CL/F and Vc/F. Bupropion F was higher in women when compared with men, with an estimate of 1.20 (1.08, 1.37) relative to men. There was an almost 50% probability of bupropion bioavailability for females being greater than 125% of the typical male, suggesting that sex may have an influence on bupropion first-pass metabolism. The 95% CI for the age effect on CL/F was not distinguishable from the null value, and the probability for subjects to fall outside the 80% to 125% reference range was minimal. Therefore, age is not likely to be an important covariate for bupropion CL/F. Race effects on CL/F were poorly defined and not estimated with sufficient precision to make definitive statements concerning effects. Race was also found to be an important covariate for determination of bupropion CL/F, but the magnitude of this effect was small and unlikely to be clinically meaningful with non-white subjects having a CL/F that was within 20% of that observed in white subjects.

Hydroxybupropion:

- A one-compartment model with zero-order drug delivery to the depot compartment and subsequent first-order absorption was chosen as the hydroxybupropion model. Inter-individual random effects were incorporated for CL/F and Vc/F and between-occasion random effects were included for D1, Ka, and F.
- The typical estimates (95% CI) of PK model parameters for the reference covariate effects (white race, male, 70 kg IBW, 70 kg total body weight, 35 years) were:
  - CL/F = 12.0 (11.0, 13.2) L/hr,
  - Vc/F = 399 (369, 432) L,
  - Ka = 0.570 (0.511, 0.628) hr^{-1}, and
  - D1 = 1.29 (1.16, 1.42) hr.
- All of the covariate effects studied (IBW, age, race on CL/F; Weight on Vc/F; sex on F) were well defined. Age and race had no effect on hydroxybupropion CL/F, while CL/F and Vc/F increased with increasing IBW and WT respectively.

Threohydrobupropion:

- Threohydrobupropion disposition was well described by a two-compartment model with zero-order drug delivery to the depot compartment and subsequent first-order absorption. Inter-individual random effects were incorporated for CL/F and Vc/F and between-occasion random effects were included for D1, Ka, and F.
- The typical estimates (95% CI) of PK model parameters for the reference covariate effects (white race, male, 70 kg IBW, 35 years) were:
  - CL/F = 27.6 (23.3, 32.9) L/hr,
  - Vc/F = 732 (570, 914) L,
  - Vp/F = 904 (784, 1033) L,
  - Q/F = 83.9 (71.3, 97.2) L/hr,
  - Ka = 0.368 (0.317, 0.423) hr^{-1}, and
  - D1 = 1.86 (1.71, 2.05) hr.
- Race, age, and sex are not likely to have a meaningful effect on threohydrobupropion PK, given the inclusion of the null value in the CI, the precise estimate of the effect, and the low probability that F values are different in females when compared to males. The remaining covariates studied (IBW on CL/F and Vc/F) were poorly defined and not estimated with sufficient precision to make definitive statements concerning these covariate effects.

Erythrohydrobupropion:

- Erythrohydrobupropion disposition was described by a one-compartment model with zero-order drug delivery to the depot compartment and subsequent first-order absorption. Inter-individual random effects were incorporated for CL/F and Vc/F and no between-occasion random effects were estimated.
- The typical estimates (95% CI) of PK model parameters for the reference covariate effects (white race, male, 70 kg IBW, 35 years) were:
  - CL/F = 162 (138, 190) L/hr,
  - Vc/F = 7040 (6180, 8060) L,
  - Ka = 0.548 (0.476, 0.610) hr^{-1}, and
  - D1 1.95 (1.66, 2.19) hr.
- The 95% CI for the age and race effects on CL/F were not distinguishable from the null values and the probability densities were generally contained within the 80% to 125% reference range. The same was true for sex on erythrohydrobupropion bioavailability. Therefore, age, race, and sex are not likely to have a clinical impact on erythrohydrobupropion PK. The remaining covariates studied (IBW on CL/F and Vc/F) were poorly defined and not estimated with sufficient precision to make definitive statements concerning these covariate effects.

The PK model evaluation results, which included the results of an external predictive check and a nonparametric bootstrap for each model, revealed that the final models provided a reliable description of the data with good precision of structural model and variance parameter estimates.

The models developed from Phase 1 data provided a reasonable description of Naltrexone and Bupropion PK in the NB303 study. Estimates for the smoking effect on CL/F were 0.906 (0.768, 1.04), 0.608 (0.332, 0.884), 0.963 (0.872, 1.05), 0.938 (0.758, 1.12), 1.03 (0.730, 1.33), and 1.11 (0.887, 1.33) for naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion respectively.

According to the Sponsor's Analysis from Phase 3 Data:
The study population consisted of 59 males and 331 females with ages ranging from 19 to 65 years and weights ranging from 66 to 168 kg. Similar to the phase 1 studies, the majority of subjects were white. The continuous covariates, weight, BMI, and CRCL, were positively correlated with correlation coefficients of at least 0.56 (Table 6). Males had higher body weights and IBW when compared to females, but were relatively equivalent for body mass index (BMI) and age. African American and white patients demonstrated covariate distributions that were not notably different, with the exception of whites being older. Other race categories were largely underrepresented in the NB303 data set.

Table 6. Summary of Continuous Covariates and their correlation: Modeling Data Set, NB-303

Covariate	N	Minimum	Maximum	Median	Mean	SD
Age (y)	390	19.0	65.0	46.0	45.6	10.90
Weight (kg)	390	66.0	168.0	98.0	100.0	16.20
Body Mass Index (kg/m^2)	390	24.7	45.4	33.8	34.6	4.30
Ideal Body Weight (kg)	390	40.6	100.0	57.8	59.4	8.99
Creatinine CL (mL/min)	390	52.7	270.0	116.0	120.0	33.40
AST (U/L)	390	8.0	102.0	19.0	20.7	8.18
ALT (U/L)	390	2.0	103.0	21.0	24.1	13.00

	Age	Weight	BMI	IBW	CRCL	AST	ALT
Age	1.000	−0.153	−0.150	−0.084	−0.575	0.060	−0.044
Weight	−0.153	1.000	0.748	0.678	0.646	0.046	0.173
BMI	−0.150	0.748	1.000	0.059	0.559	−0.037	0.096
IBW	−0.084	0.678	0.059	1.000	0.405	0.117	0.188
CRCL	−0.575	0.646	0.559	0.405	1.000	−0.005	0.156
AST	0.060	0.046	−0.037	0.117	−0.005	1.000	0.696
ALT	−0.044	0.173	0.096	0.188	0.156	0.696	1.000

Table 7. Summary of Categorical Covariates in NB-303

	Gender		**Race**					
	Female	Male	White	AA	Asian	PI	AI	Other
Number	331	59	349	33	4	1	1	1
Percentage	85	15	89	8	1	< 1	< 1	< 1

AA = African American, PI = Pacific Islander, AI = American Indian or ALaska Native

Although covariate model parameters were fixed to the values obtained in the Phase 1 analysis, plots of the mean observed trough concentration for individual patients versus covariate values were generally consistent with covariate models obtained from the Phase 1 PK analysis, though some differences were evident. For example, no clear race effects were observed for NB-303 trough concentrations. Trough concentrations were comparable when comparing smokers to non-smokers across all analytes.

Population PK models were also fit to the NB-303 study data while estimating CL/F and covariate effects on CL/F only. Results using this methodology were mixed. While CL/ F estimates for some analytes were reasonably similar to the Phase 1 estimates, some analyte fits were problematic. For example, for 6-beta-naltrexol, the effect of smoking on CL/F was 0.608 for the Phase 1 model and was estimated to be 1.00 for the Phase 3 model fit.

Estimates for the smoking and creatinine clearance effect on CL/F for naltrexone, 6-beta-naltrexol, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion are summarized in *Table 8* below. The 95% CIs were calculated using the NONMEM standard error estimates.

Estimated creatinine clearance was not included as a covariate in the phase 1 analysis, due to lack of subjects with reduced renal function. Study NB-303 included subjects with reduced renal function, with estimated creatinine clearance values approaching 50 mL/min.

Table 8. Summary of Smoking and Creatinine Clearance Effect on CL/F in NB-303

Analyte	Smoking effect on CL/F Exponent (95% CI)	Creatinine clearance effect on CL/F Exponent (95% CI)
Naltrexone	0.91 (0.77, 1.04)	0.05 (-0.18, 0.28)
6-beta-naltrexol	0.61 (0.33, 0.88)	0.57 (0.45, 0.69)
Bupropion	0.96 (0.87, 1.05)	-0.03 (-0.14, 0.08)
Hydroxybupropion	0.94 (0.76, 1.12)	0.01 (-0.12, 0.14)
Threohydrobupropion	1.03 (0.73, 1.33)	0.27 (0.11, 0.43)
Erythrohydrobupropion	1.11 (0.887, 1.33)	0.37 (0.25, 0.50)

Given these results, renal function likely has little effect on naltrexone, bupropion, and hydroxybupropion CL/F over the creatinine clearance range of 53-150 mL/min (capped at 150 mL/min). Threohydrobupropion and erythrohydrobupropion demonstrated a well-defined decrease in CL/F with decreasing renal function, with a decrease of 17% and 23% respectively in a typical subject with an estimated creatinine clearance of 50 mL/min when compared to a subject with an estimated creatinine clearance of 100 mL/min. For 6-beta-naltrexol, the effect of renal function was more pronounced with a CL/F value that is 33% less than reference for a typical subject with a 50 mL/min estimated creatinine clearance.

Please refer to the following link for details on the population analysis report in EDR. ***\\Cdsesub1\EVSPROD\NDA200063\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\metrum-1***

4 REVIEWER'S ANALYSIS

4.1 Introduction

The general approach followed in sponsor's population PK analysis is acceptable. The key points regarding the reviewer's analysis are mentioned below.

4.2 Objectives

Analysis objectives are:

- The population pharmacokinetic analysis was repeated to verify the sponsor's analysis.

4.3 Methods

4.3.1 Data Sets

Reviewer's population PK analysis was performed using sponsor's data-sets. The data sets submitted with the original NDA submission were not correct and unusable. Acknowledging the errors in the datasets, the sponsor's submitted revised data sets.

Data sets used are summarized in Table 9.

Table 9. Analysis Data Sets

Study Number	Name	Link to EDR
Pooled phase 1 studies	buprop.xpt, hydroxy.xpt, erythro.xpt, threo.xpt, naltrex.xpt, beta.xpt,	\\Cdsesub1\EVSPROD\NDA200063\0012\m5\datasets\metrum-1\analysis\programs
NB-303	nb303d.xpt	\\Cdsesub1\EVSPROD\NDA200063\0012\m5\datasets\metrum-1\analysis\programs

4.3.2 Software

Data-set for the analysis was prepared using SAS v 9.2. NONMEM Version VI was used for the analysis and run using Wings for NONMEM VI on a Dell Latitude E6400 computer, equipped with a G77 Fortran compiler. The diagnostic and other plots were generated using PKTOOL R-script.

4.3.3 Models

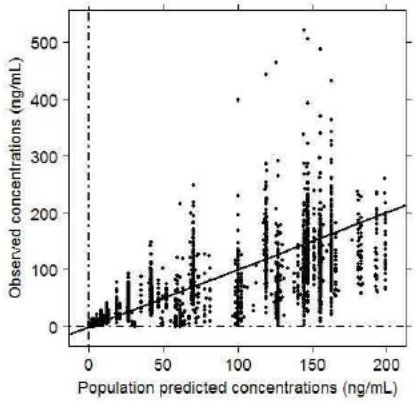
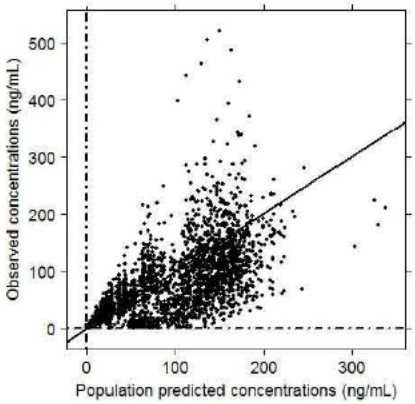
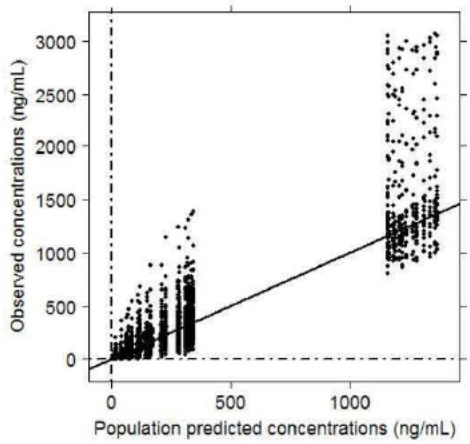
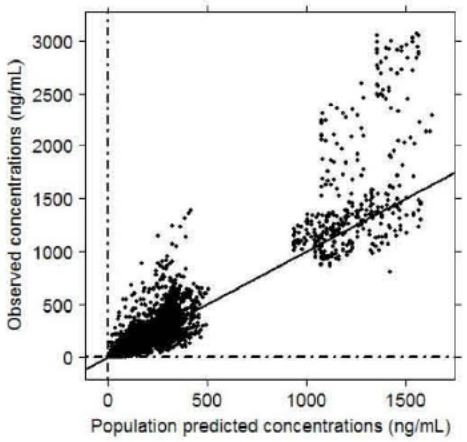
The base model of the sponsor (one-compartment model with first-order absorption and first-order elimination with IIV on CL and V) was used. Graphical analysis of the base model output (goodness-of-fit plots and Eta-covariate plots) was used to evaluate the adequacy of the model and selection of covariates for further evaluation.

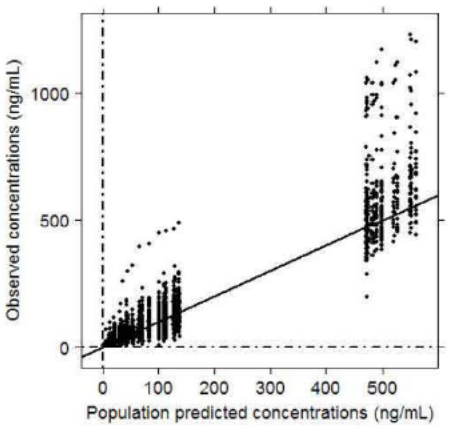
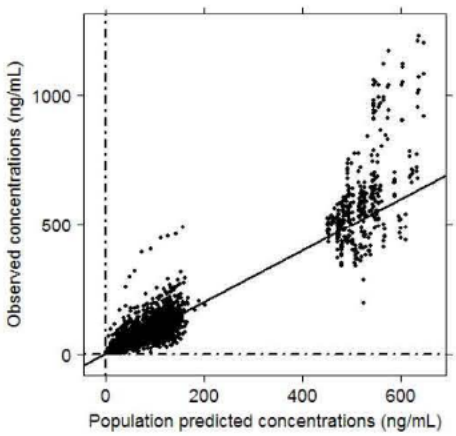
4.4 Results

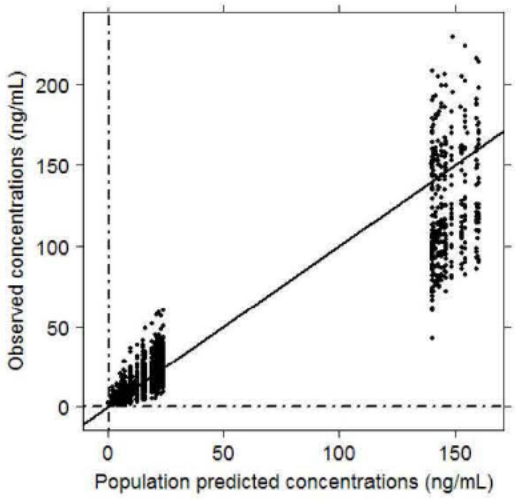
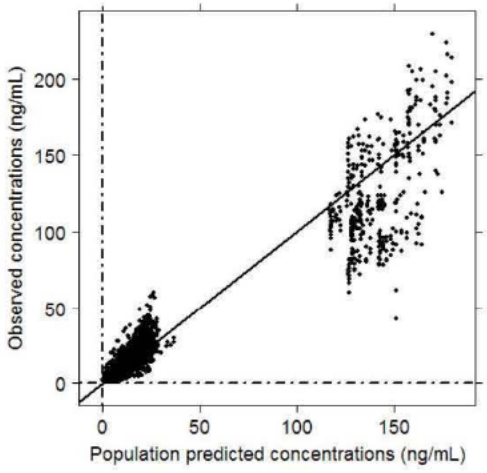
4.4.1 Population pharmacokinetics

The structural models developed by the sponsor for each of the six analytes are reasonable and acceptable. The incorporation of between occasion variability in absorption related parameters (F1, Ka and D1) was important for structural models for all analytes. The representative goodness-of-fit plots from the base and full models are shown below in Figure 15 for bupropion, naltrexone and their respective metabolites.

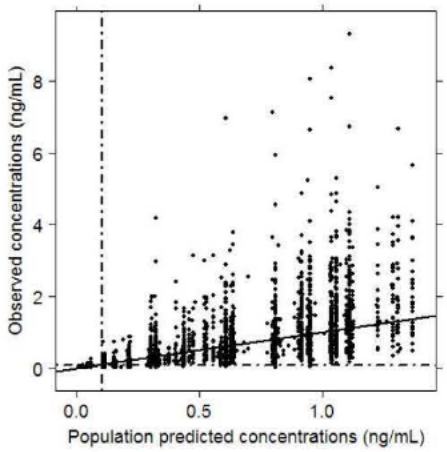
Figure 15. Diagnostic plots from the base and full model

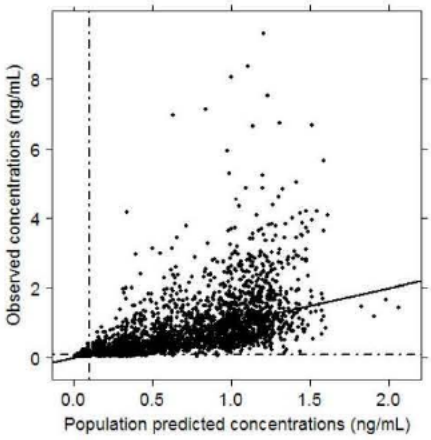
Base Model	Full Model
(a) Observed versus population predicted (**bupropion**)	(b) Observed versus population predicted (**bupropion**)
	
Base Model	**Full Model**
(a) Observed versus population predicted (**hydroxybupropion**)	(b) Observed versus population predicted (**hydroxybupropion**)
	

Base Model	Full Model
(a) Observed versus population predicted (**threohydrobupropion**) 	(b) Observed versus population predicted (**threohydrobupropion**) 

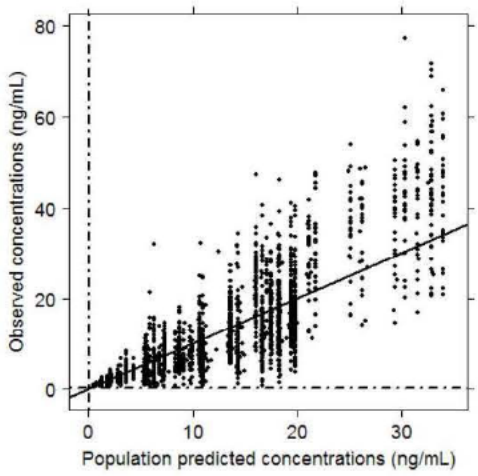
Base Model	Full Model
(a) Observed versus population predicted (**erythrohydrobupropion**) 	(b) Observed versus population predicted (**erythrohydrobupropion**) 

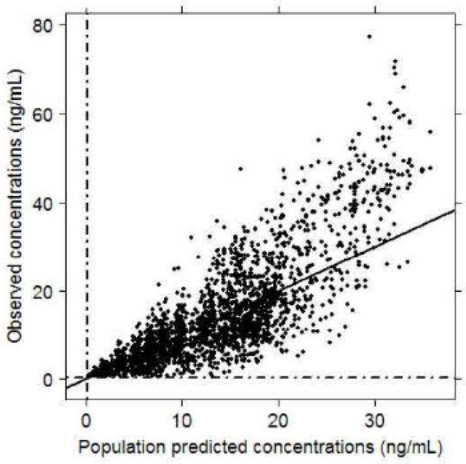
Base Model	Full Model
(a) Observed versus population predicted (**naltrexone**)	(b) Observed versus population predicted (**naltrexone**)





Base Model	Full Model
(a) Observed versus population predicted (**6-beta naltrexol**)	(b) Observed versus population predicted (**6-beta naltrexol**)



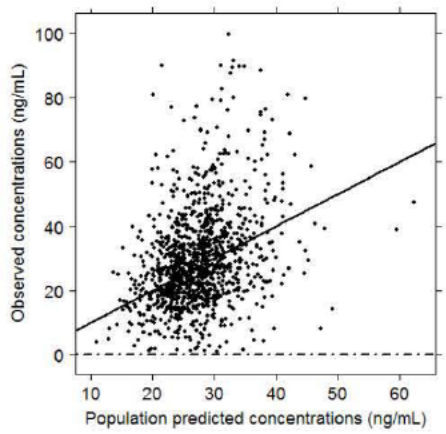


As illustrated in the figure above, overall the incorporation of covariates did explain the inter-individual variability in most of the cases, except hydroxybupropion, threohydrobupropion and naltrexone where there was some under prediction at higher concentrations. This variability could not be explained by any of the covariates.

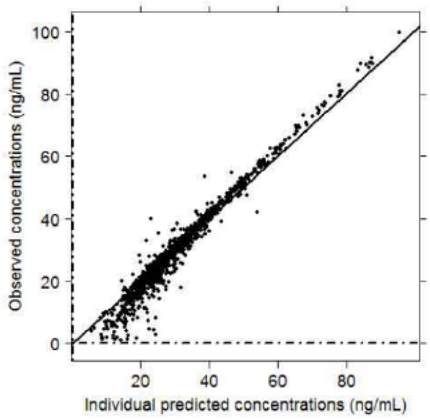
Sponsor's results regarding creatinine clearance from the Phase 3 data were also confirmed in the reviewer's analysis.

Figure 16. Diagnostic plots from the sponsor's full models for bupropion, hydroxy-, threohydro-, and erythrohydro-bupropion

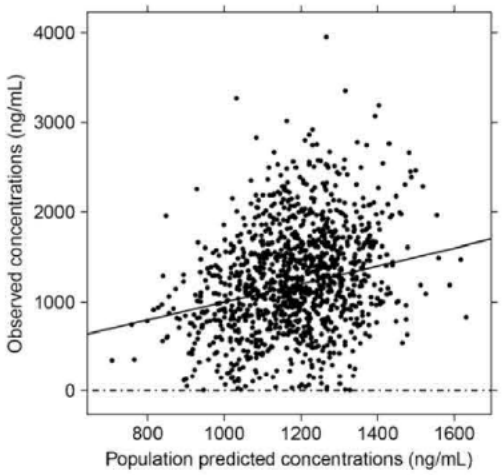
(a) Observed versus population predicted (**bupropion**)



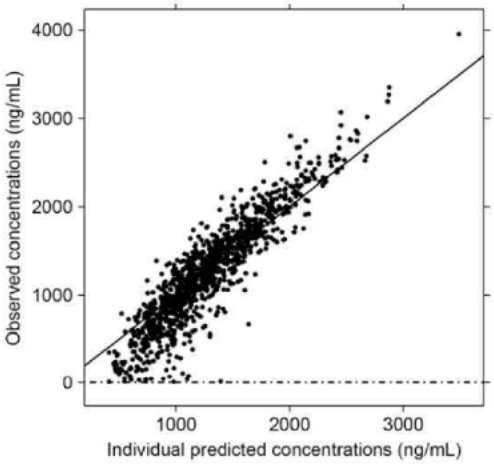
(b) Observed versus individual predicted (**bupropion**)



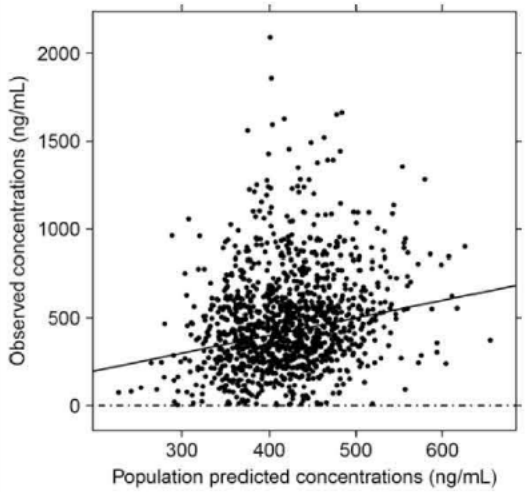
(c) Observed versus population predicted (**hydroxybupropion**)



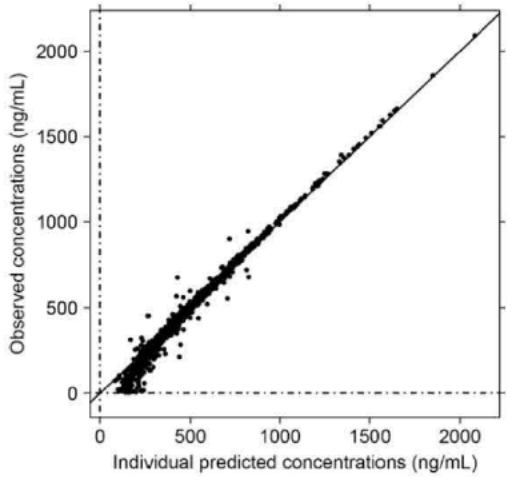
(d) Observed versus individual predicted (**hydroxybupropion**)



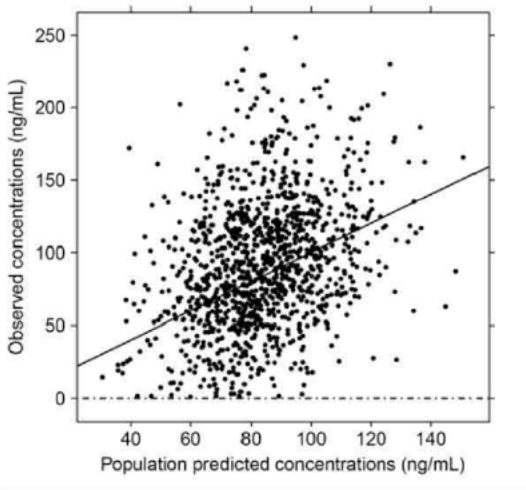
(e) Observed versus population predicted (**threohydrobupropion**)



(f) Observed versus population predicted (**threohydrobupropion**)



(g) Observed versus population predicted (**erythrohydrobupropion**)



(h) Observed versus individual predicted (**erythrohydrobupropion**)

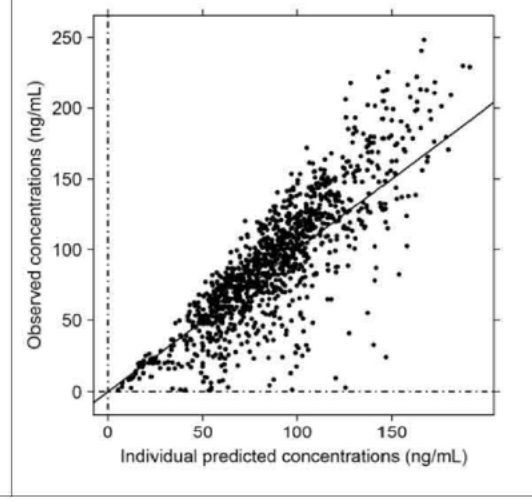
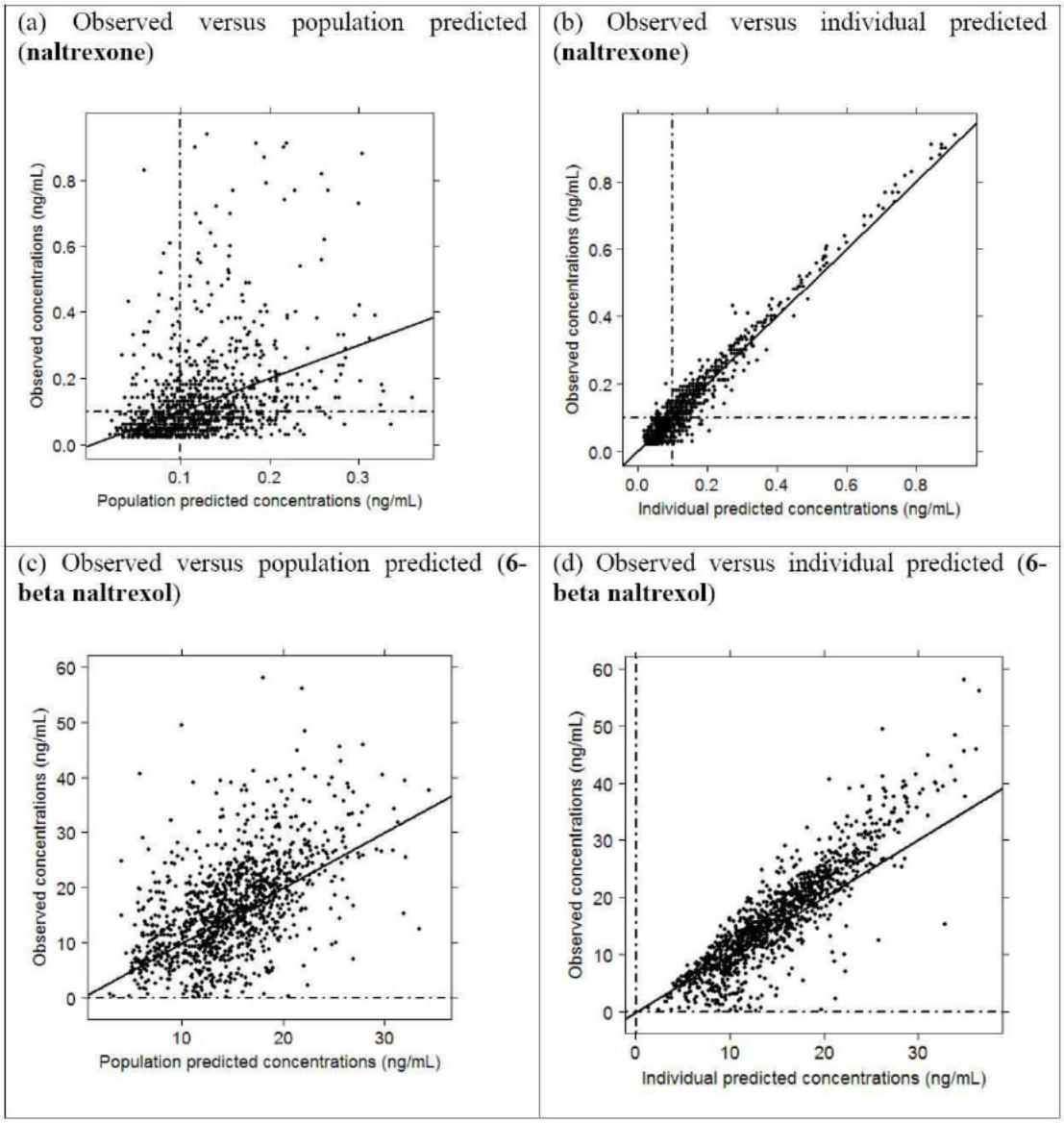


Figure 17. Diagnostic plots from the sponsor's full models for naltrexone and 6-beta naltrexoll



The creatinine clearance was linearly correlated with ideal body weight (Figure 16). Therefore, the ideal body weight adjusted clearance was plotted against creatinine clearance for all the analytes. The plots show that except bupropion and naltrexone, ideal body weight adjusted clearance showed linear increase with creatinine clearance. The most prominent relationship was evident for 6-beta naltrexol whereas, hydroxybupropion, erythrohydrobupropion and threohydrobupropion showed relatively a shallower increase for the ideal body weight clearance (Figure 17).

Figure 18. Linear correlation of creatinine clearance with ideal body weight in Trial NB-303 PK dataset

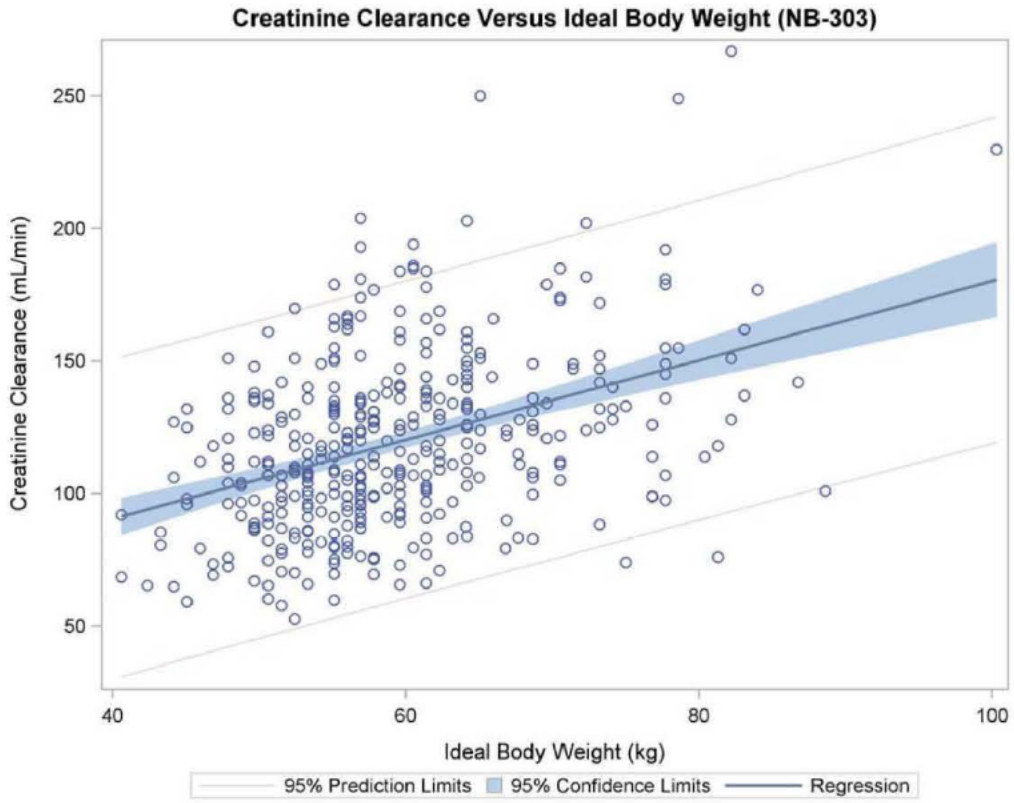
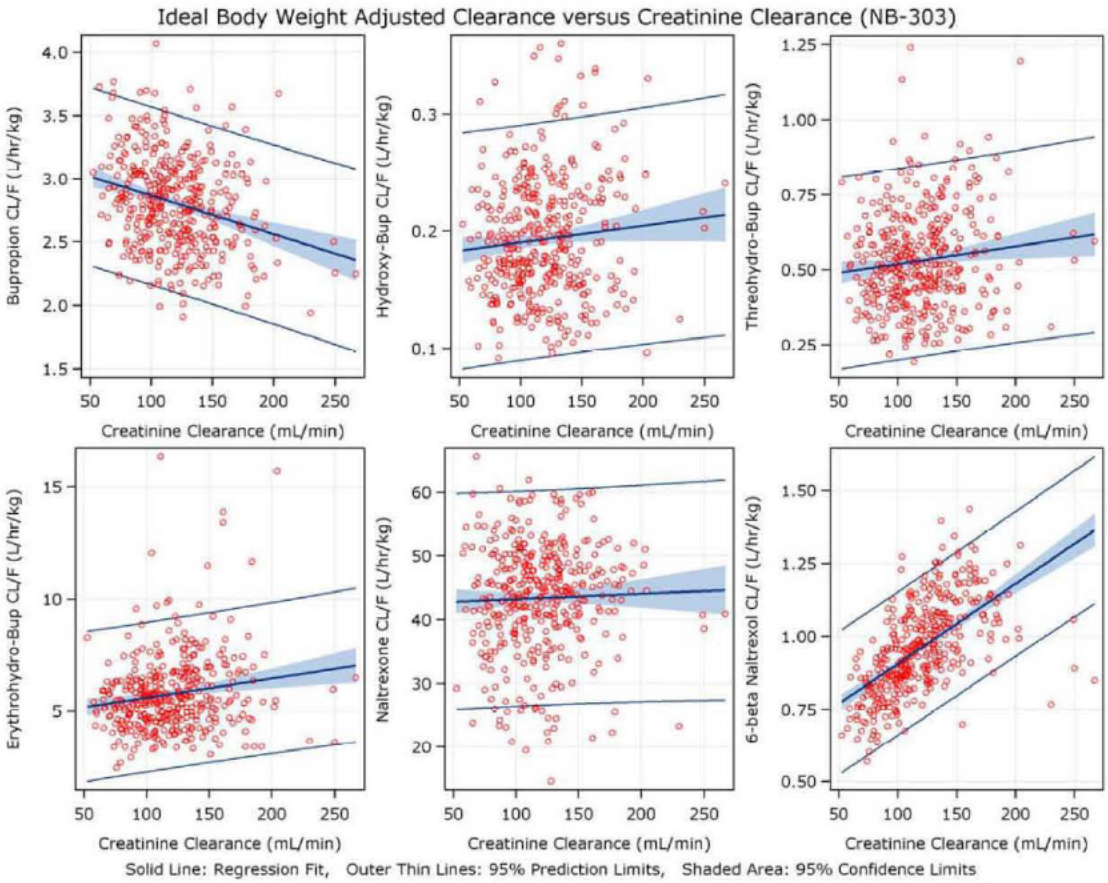


Figure 19. Ideal body weight adjusted clearance versus creatinine clearance for different analytes in Trial NB-303 PK dataset



5 APPENDIX

5.1 Listing of Analyses Codes and Output Files

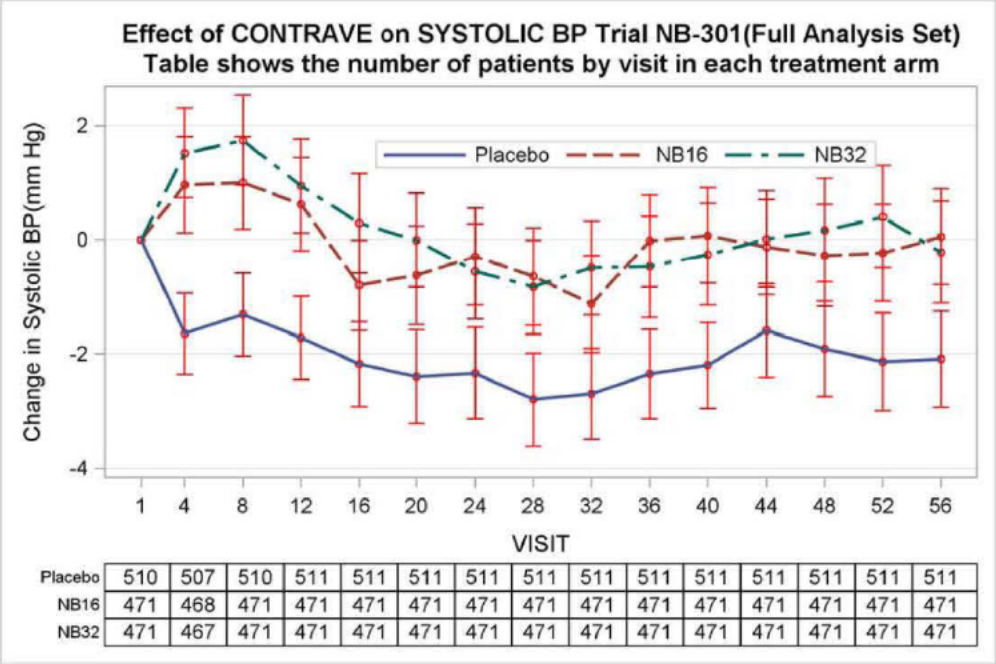
Analyte Name/ Data-set Name	Model File Name	Output Folder Name	Description	Location in \\cdsnas\pharmacometrics\
Bupropion / Bup.csv Nb303d.csv	Run5.ctl	Run5.g77, Run5out	Base Model	NDA200063\PM\BUP
	Run11.ctl	Run11.g77, Run11out	Full Model	
	Run600.ctl	Run600.g77, Run600out	Full Model (NB-303)	
Hydroxybupropion / Hydroxy.csv Nb303d.csv	Run111.ctl	Run111.g77, Run111out	Base Model	
	Run112.ctl	Run112.g77, Run112out	Full Model	
	Run601.ctl	Run601.g77, Run601out	Full Model (NB-303)	
Threohydrobupropion / Threo.csv Nb303d.csv	Run204.ctl	Run204.g77, Run204out	Base Model	
	Run205.ctl	Run205.g77, Run205out	Full Model	
	Run602.ctl	Run602.g77, Run602out	Full Model (NB-303)	
Erythrohydrobupropion/ Erythro.csv Nb303d.csv	Run304.ctl	Run304.g77, Run304out	Base Model	
	Run305.ctl	Run305.g77, Run305out	Full Model	
	Run603.ctl	Run603.g77, Run603out	Full Model (NB-303)	
Naltrexone / Naltrex.csv Nb303d.csv	Run22.ctl	Run22.g77, Run22out	Base Model	NDA200063\PM\NAL
	Run23.ctl	Run23.g77, Run23out	Full Model	
	Run502.ctl	Run502.g77, Run502out	Full Model (NB-303)	
6beta-naltrexol / Beta.csv Nb303d.csv	Run107.ctl	Run107.g77, Run107out	Base Model	
	Run108.ctl	Run108.g77, Run108out	Full Model	
	Run602.ctl	Run602.g77, Run602out	Full Model (NB-303)	

Analysis Name	Trial/SAS Data-set Name	SAS Code File Name	Description	Location of SAS Code in \\cdsnas\pharmacometrics\
DR-Efficacy	dm.xpt, vs.xpt	NB201.sas	Dose-response analysis from trial NB201	NDA200063\PM\DR\Efficacy
	adcfbvse.xpt	NB301.sas	Dose-response analysis from trial NB301	
Exposure-Weight loss	adcfbwte.xpt, pc.xpt,	NB303WTLOSS.sas 303WTLOSSPKYNO.sas	Exposure-wt. loss analysis from Phase 3 trial NB-303	
DR-Safety (BP)	NB301/adcfbvse.xpt, NB302/adcfbvs.xpt,	301adcfbvse_BloodP.sas 302adcfbvs_BloodP.sas	Analysis for BP from Phase 3 trials	NDA200063\PM\DR\Safety
DR-Safety (BP)	NB301/adcfbvse.xpt, NB302/adcfbvs.xpt, NB303/adcfbvse.xpt, NB304/adcfbvse.xpt,	PooledP3_BP.sas	Pooled analysis for BP from Phase 3 trials	
Exposure-AE	NB303/adae.xpt, pc.xpt	nb303aeanalysisfnl.sas	Exposure AE from trial NB-303	
Serum Creatinine		NB301lab.sas	Serum creatinine plot	

5.2 Trial Specific Data on Dose-Safety for Blood Pressure

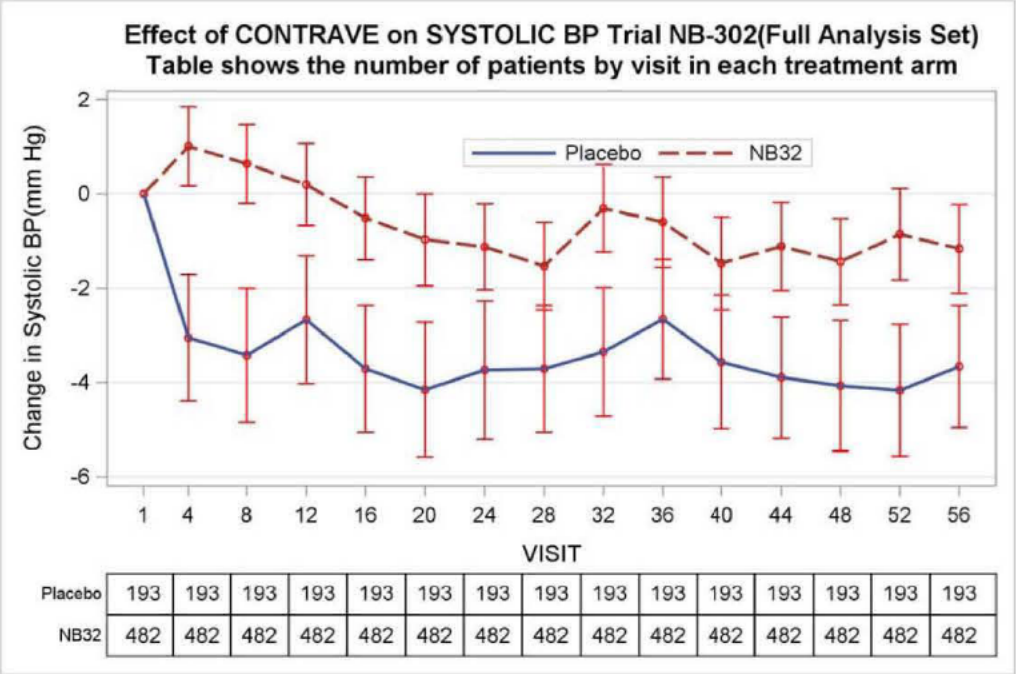
Contrave treatment was associated with an increase in systolic blood pressure (BP) in obese patients. Data from placebo controlled Trial NB-301 showed that the maximum mean increase of around 1 to 2 mm Hg from baseline was observed at Visit 4 with the active treatment arms. This mean rise in systolic BP returned to baseline by week 16. The placebo group showed greater reduction in BP from baseline. Therefore, the beneficial effect of weight loss in terms of reduction in BP was absent in the Contrave treatment group in Trial NB-301.

Figure 20. Change in Systolic Blood Pressure from baseline (Mean±SE) versus Time (weeks) by Treatment in Phase 3 confirmatory trials NB-301 and NB-302



Placebo	510	507	510	511	511	511	511	511	511	511	511	511	511	511	511
NB16	471	468	471	471	471	471	471	471	471	471	471	471	471	471	471
NB32	471	467	471	471	471	471	471	471	471	471	471	471	471	471	471

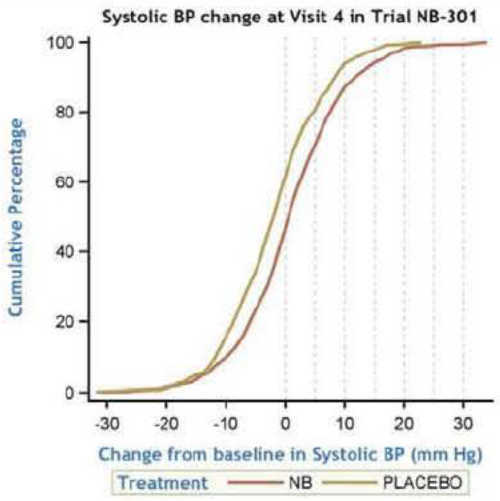
(b) NB-302



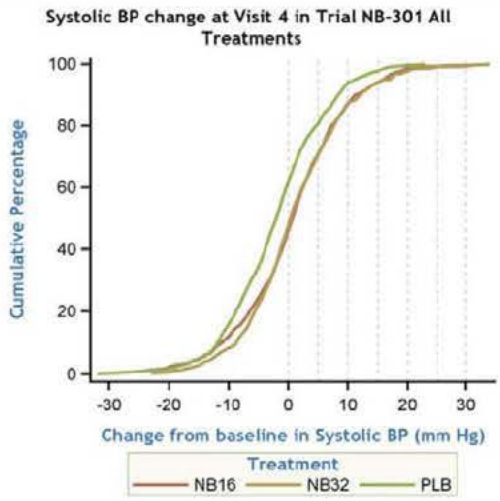
To determine the risk to patients with respect to the maximum BP increase, cumulative percentage of subjects were plotted versus the change in BP for the pooled active (NB16 and NB32) versus the placebo treatment, and by individual treatment arms (NB16, NB32, and placebo), both at week 4 and 8. The plots clearly showed a distinction between the placebo and active treatment arms (shift to the right) (Figure 10). Trial NB-302 patients showed a similar trend (Figure 11). Based on the cumulative frequency distribution top 5% of patients in the Contrave treatment arm had 16 mm Hg increase from baseline versus 11 mm Hg for the top 5% placebo subjects; an overall risk of 5 mm Hg increase against placebo. This difference against placebo was around 3 mm Hg in another Trial NB-303 (Figure 12).

Figure 21. Cumulative Percentage of Subjects versus Systolic BP Change from Baseline by Treatment in Phase 3 confirmatory trial (NB-301)

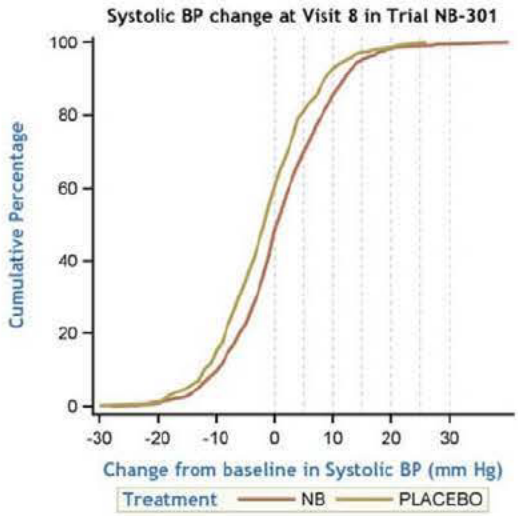
(a) Visit 4 – Pooled Active versus Placebo



(b) Visit 4 – All Active versus Placebo



(c) Visit 8 – Pooled Active versus Placebo



(d) Visit 8 – All Active versus Placebo

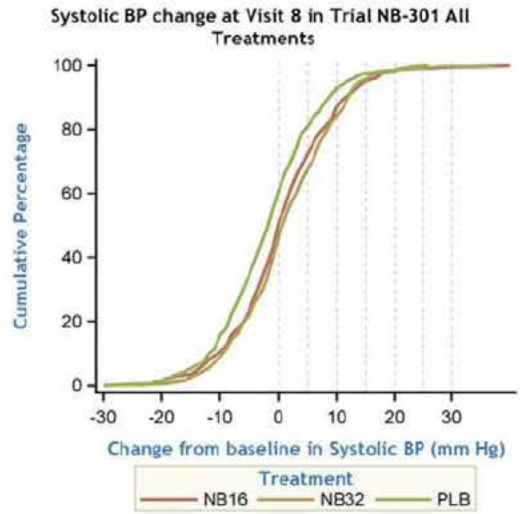


Figure 22. Cumulative Percentage of Subjects versus Systolic BP Change from Baseline by Treatment in Phase 3 confirmatory trial (NB-302)

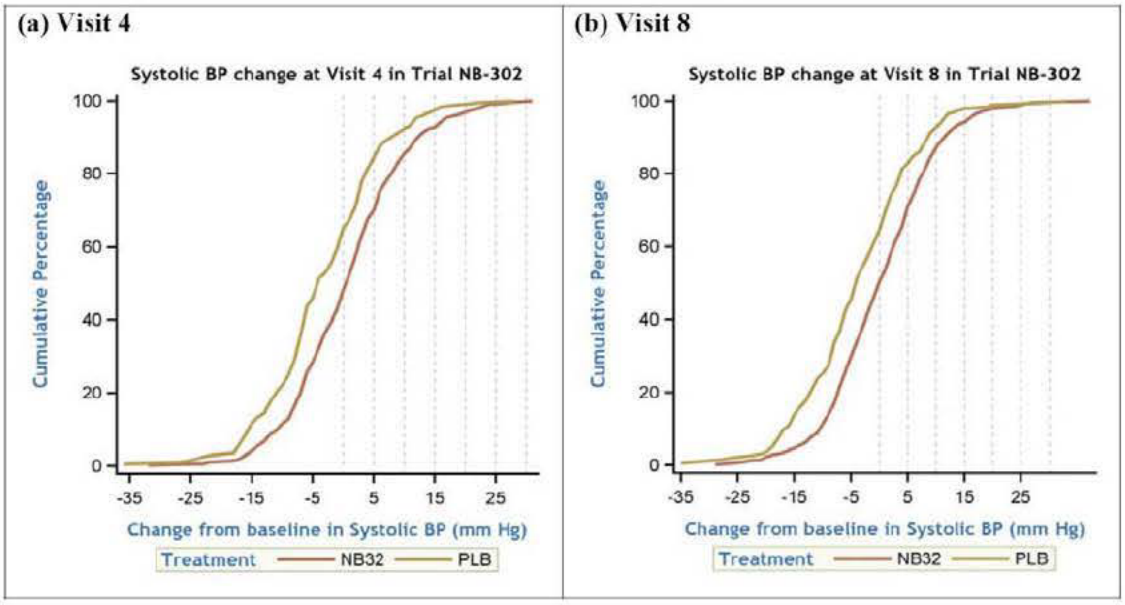
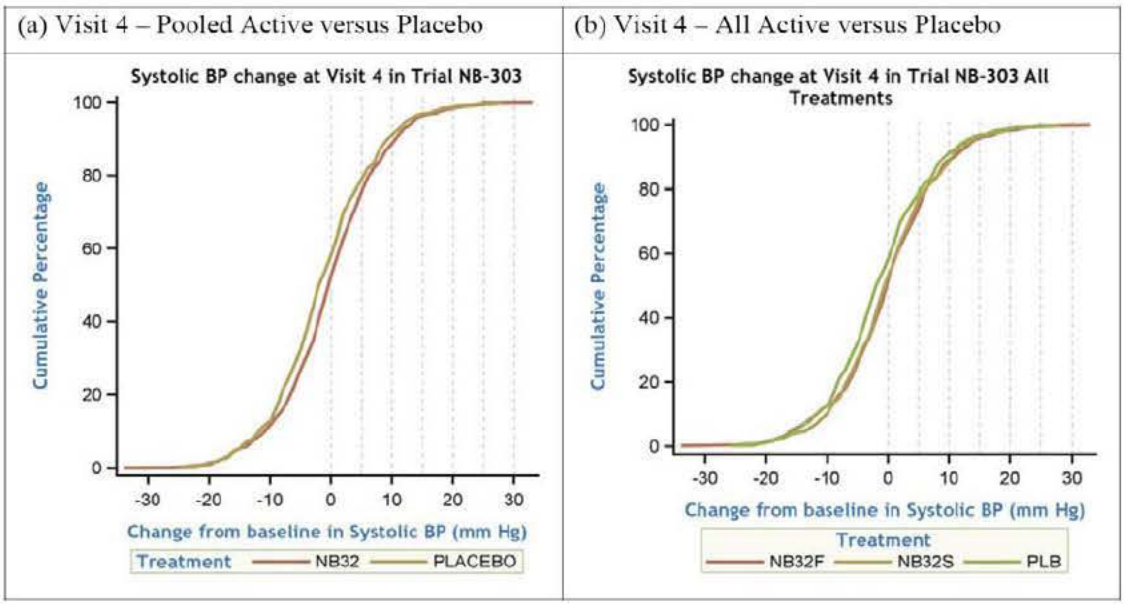


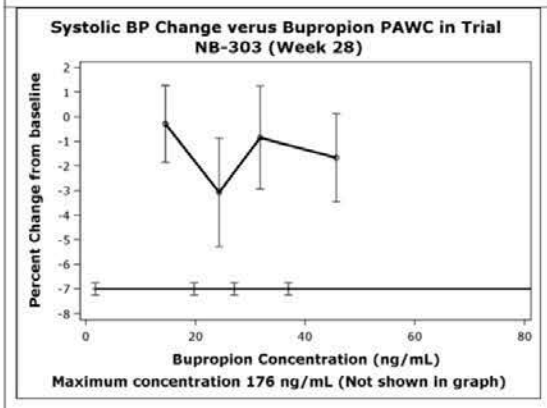
Figure 23. Cumulative Percentage of Subjects versus Systolic BP Change from Baseline by Treatment in Phase 3 confirmatory trial (NB-303)



Mean change in Systolic BP from baseline in Trial NB-303, however, did not show any trend with increasing bupropion exposure, when plotted cross the median of each quartile for bupropion or bupropion PAWC metric (Figure 13).

Figure 24. Exposure-Response for Systolic BP Change

(a) Bupropion – SBP Relationship



(b) Bupropion PAWC – SBP Relationship

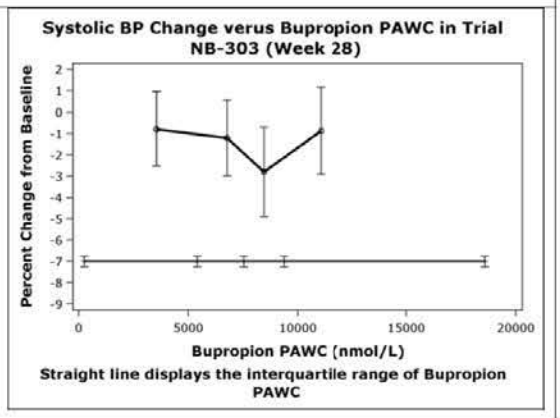
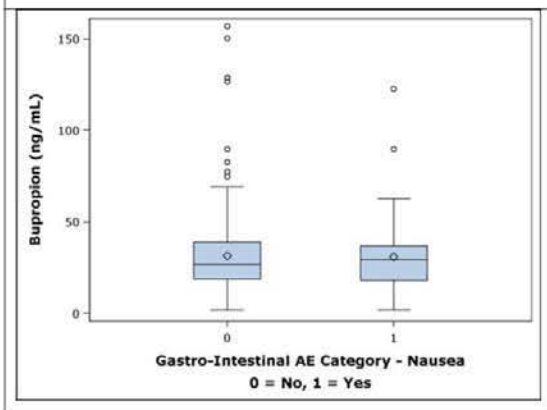
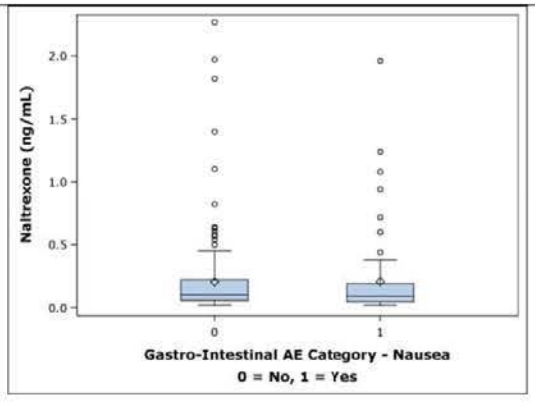


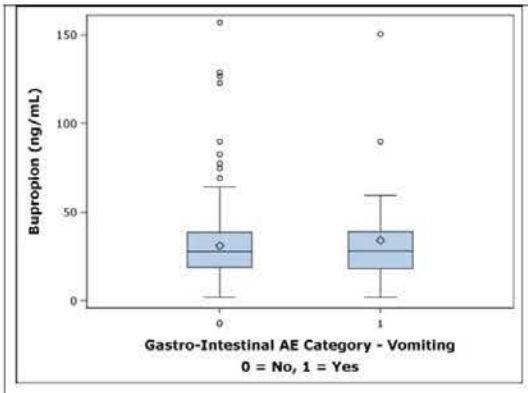
Figure 25. Exposure comparison among subjects with and without Treatment Emergent Adverse Events in Phase 3 confirmatory trial (NB303)

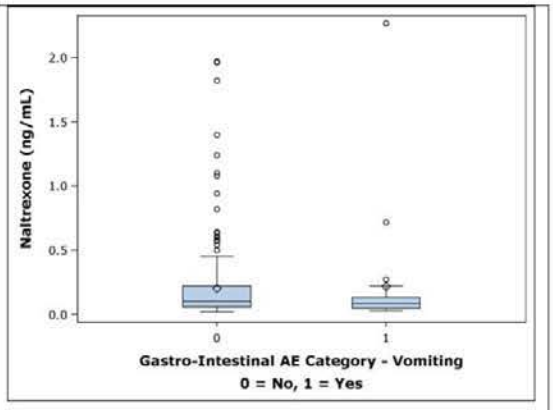
(A) Nausea



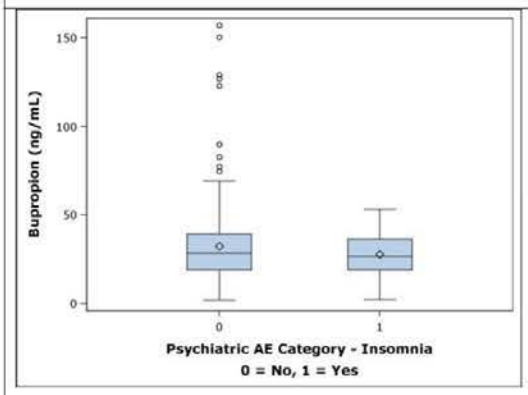


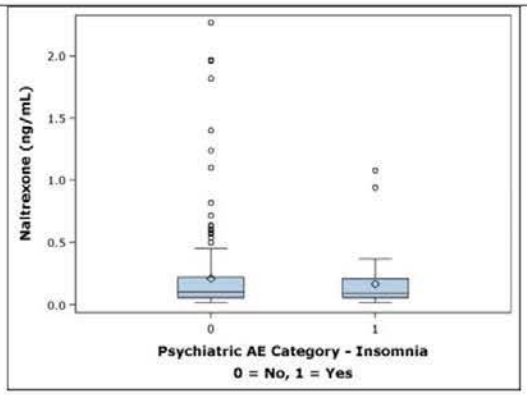
(B) Vomiting



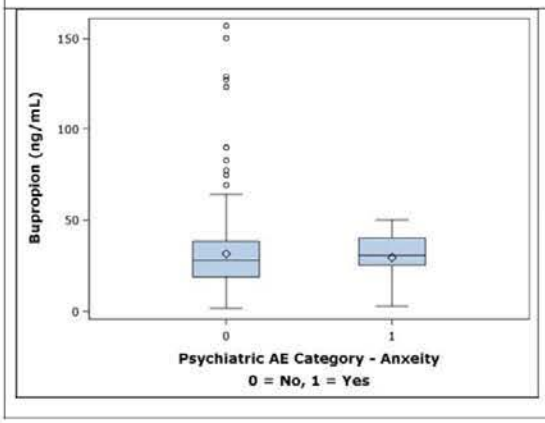


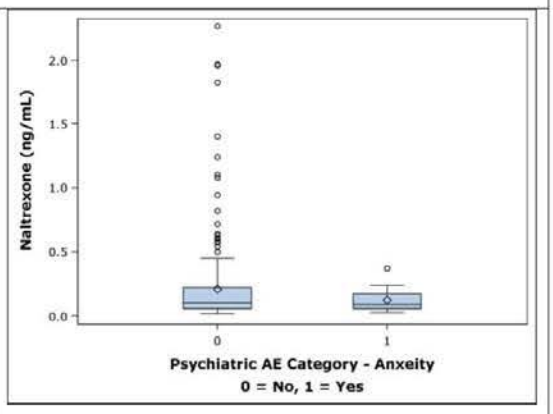
(C) Insomnia

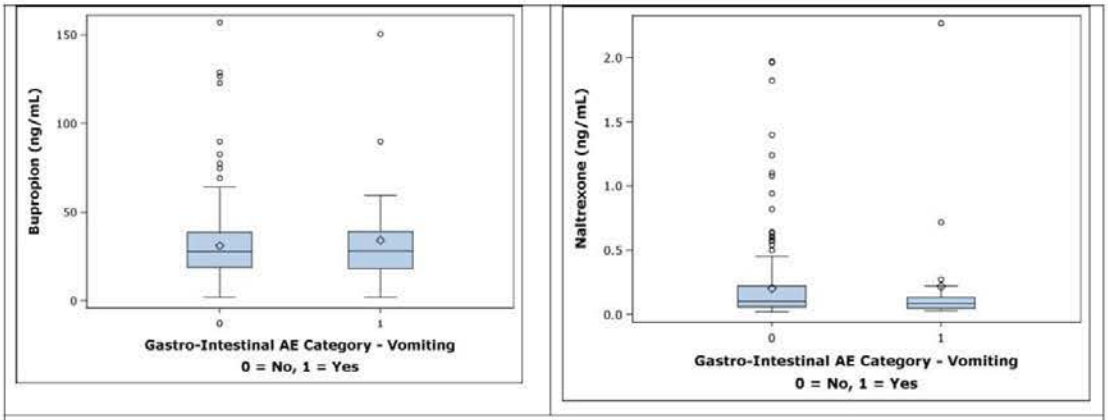




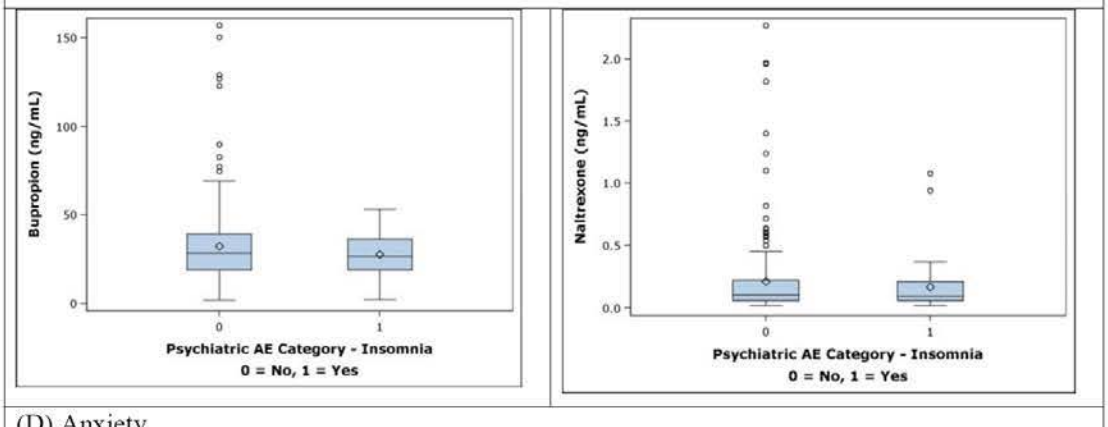
(D) Anxiety



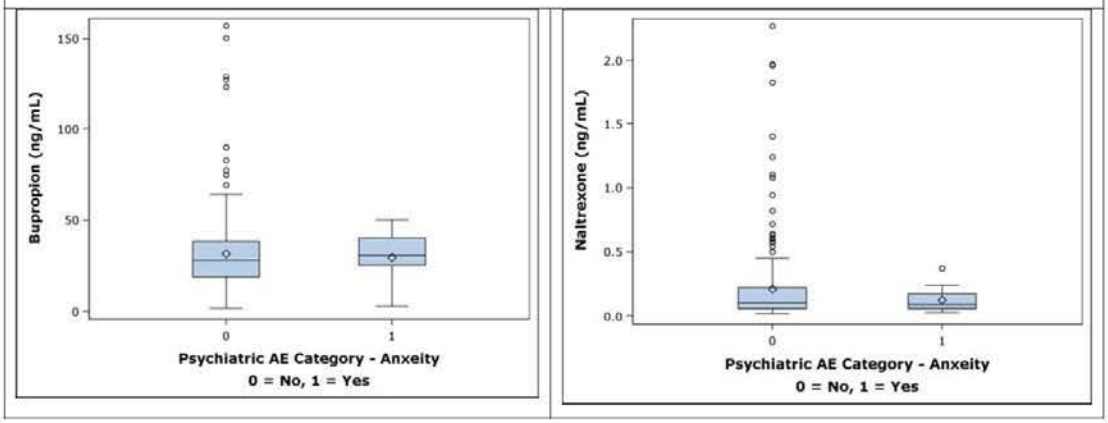




(C) Insomnia



(D) Anxiety



4.3 Pharmacogenomics Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA Number	200,063
Submission Date	31 Mar 2010
Applicant Name	Orexigen Therapeutics, Inc.
Generic Name	Naltrexone SR/Bupropion SR
Proposed Indication	Management of obesity, including weight loss and maintenance of weight loss, in patients with an initial body mass index ≥30 kg/m2 or ≥27 kg/m2 with one or more risk factors (e.g. diabetes, dyslipidemia, or hypertension)
Primary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

1 Background

The current submission is a NDA for naltrexone SR/bupropion SR (NB) to be indicated for the management of obesity. The proposed target dose is (b) (4) naltrexone and 360 mg bupropion divided twice daily, which is titrated up from 8 mg naltrexone and 90 mg bupropion once daily over four weeks. The proposed dose of bupropion is higher than the doses generally recommended for depression and smoking cessation (usual dose 300 mg daily, maximum dose 450 mg daily). Intrinsic factors that result in high bupropion exposure may alter the risk/benefit profile (e.g., seizure risk).

CYP2B6 metabolizes bupropion to hydroxybupropion (Hsyu, et al. J Clin Pharmacol 1997). CYP2B6 is highly polymorphic. Over a dozen alleles that exhibit reduced activity or transcription relative to the wild-type allele (www.cypalleles.ki.se) have been identified, which may contribute to interindividual variability in CYP2B6 substrate exposure.

The purpose of this review is to evaluate whether CYP2B6 polymorphisms are likely to result in clinically relevant increases in bupropion exposure.

2 Submission Contents Related to Genomics

The NB clinical development program consists of 23 trials, including 15 Phase 1, four Phase 2, and four pivotal Phase 3 studies. The applicant has not included any pharmacogenomic studies in the current submission. Blood samples for candidate gene analysis were collected on a voluntary basis at baseline in the Phase 3 trials (NB301, NB302, NB303, NB304) to investigate the relationship between expression levels of candidate genetic markers and the response to treatment based on selected measures of efficacy and safety. No genotyping data or reports were included in the current submission. Samples will be destroyed within 10 years of study completion.

3 Key Questions and Summary of Findings

3.1 Do CYP2B6 gene variants result in differential exposure to bupropion and/or hydroxybupropion?

Few studies have evaluated the CYP2B6-bupropion pharmacogenetic interaction. In a published study (Kirchheiner, et al. Pharmacogenetics 2003), bupropion PK following a single 150 mg dose was evaluated in 121 healthy male volunteers according to the following amino acid-changing polymorphisms: R22C, Q172H, S259R, K262R and R487C. Population PK analysis revealed that total bupropion clearance via CYP2B6 alleles *1, *2, *5 and *6 did not differ, but clearance via the *4 allele (K262R) was 1.66-fold higher compared to wild-type allele *1 (P=0.001). Carriers of the CYP2B6 *4 allele had significantly higher C_{max} of hydroxybupropion compared to all other genotypes (P=0.03). The results are summarized in the tables below.

Table 1. **CYP2B6 genotype-specific clearance of bupropion (single 150 mg dose; from Kirchheiner, et al. Pharmacogenetics 2003)**

Table 2. **CYP2B6 genotype-specific PK parameters for hydroxyburpopion (single 150 mg dose; from Kirchheiner, et al. Pharmacogenetics 2003)**

The *4 variant has been associated with lower expression of CYP2B6, but higher activity toward other substrates such as nicotine and bupropion (Zanger, et al. Pharmacogenomics 2007). In vitro studies demonstrated that carriage of the *6 allele reduces activity toward bupropion

(Desta, et al. Pharmacogenomics 2007), but such an effect was not apparent in this investigation. The authors concluded that only a minor fraction of the variability in bupropion and hydroxybupropion PK could be explained by the known CYP2B6 amino acid variants (Kirchheiner, et al. Pharmacogenetics 2003).

The intersubject variability of bupropion in Phase 1 studies of NB are summarized in the table below. The CV% following single doses of NB for Cmax and AUC were approximately 30% for bupropion and 50% for hydroxybupropion, indicating that bupropion and hydroxybupropion exposures are not excessively heterogeneous.

Table 3. Plasma PK profile of burpopion and naltrexone in pooled Phase 1 single-dose studies (2 x N8/B90)

	Arithmetic Mean ± SD (%CV)[a] [N]			
	Bupropion	**Hydroxybupropion**	**Threohydrobupropion**	**Erythrohydrobupropion**
C_{max} (ng/mL)	156 ± 49.0 (31.5%) [206]	388 ± 181 (46.6%) [154]	139 ± 54.6 (39.1%) [154]	25.7 ± 7.76 (30.2%) [154]
T_{max} (hr)	3.00 (1.00, 6.11) [206]	6.00 (3.00, 72.00) [154]	6.00 (2.00, 10.00) [154]	6.00 (3.00, 12.00) [154]
$t_{1/2}$ (hr)	21.06 ± 6.31 (30.0%) [204]	26.52 ± 7.02 (26.5%) [152]	46.81 ± 13.47 (28.8%) [146]	31.84 ± 8.64 (27.1%) [149]
AUC_{0-t} (ng·hr/mL)	1415.49 ± 462.28 (32.7%) [206]	16041.06 ± 8768.12 (54.7%) [154]	5531.86 ± 3112.88 (56.3%) [154]	1061.95 ± 429.15 (40.4%) [154]
$AUC_{0-\infty}$ (ng·hr/mL)	1486.63 ± 488.30 (32.9%) [204]	17369.91 ± 9594.63 (55.2%) [152]	6693.09 ± 3665.10 (54.8%) [146]	1240.09 ± 507.81 (41.0%) [149]

[a] T_{max} is presented as Median (Minimum, Maximum)

Abbreviations: AUC=area under the concentration-time curve from time zero until last quantifiable sample time (0-t) or extrapolated to infinity (0-∞), C_{max}=maximum plasma concentration; N=number of subjects; SD=standard deviation; $t_{½}$=apparent terminal elimination half-life; T_{max}=time to reach maximum plasma concentration; %CV=coefficient of variation.

Source: Report AA88068 (summarizing studies NB-228, NB-229, NB-230, NB-231, NB-232, NB-233, NB-234, NB-237, and NB-238) Tables 2.2.1, 2.2.2, 2.2.3, 2.2.4, 2.2.5, and 2.2.6

The *4 allele is virtually absent in Black/African populations. To the extent that this is the only allele that demonstrated influence on bupropion PK clinically, racial differences in bupropion PK would suggest a potential pharmacogenetic interaction. As shown in the table below, bupropion PK did not appear to differ in black/African-American subjects as compared to white/Caucasian subjects, suggesting that genotypic variation for *4, and other CYP2B6 alleles that differ in frequency across race groups, may not play a major role in bupropion PK.

Table 4. Plasma bupropion PK profile by race

	PK Parameter				
	Arithmetic Mean ± SD (%CV)[a] [N]				
	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
Overall	156 ± 49.0 (31.5%) [206]	3.00 (1.00, 6.11) [206]	21.06 ± 6.31 (29.95%) [204]	1415.49 ± 462.28 (32.66%) [206]	1486.63 ± 488.30 (32.85%) [204]
Race					
White or Caucasian	157 ± 50.7 (32.2%) [144]	3.00 (1.00, 6.00) [144]	20.92 ± 6.17 (29.47%) [143]	1417.44 ± 442.10 (31.19%) [144]	1491.74 ± 470.88 (31.19%) [143]
Black or African American	150 ± 47.2 (31.4%) [55]	3.00 (1.00, 6.11) [55]	21.53 ± 7.05 (32.73%) [54]	1414.93 ± 539.03 (38.10%) [55]	1479.24 ± 561.32 (37.95%) [54]
Other	162 ± 18.1 (11.2%) [7]	3.00 (1.25, 4.00) [7]	20.19 ± 2.07 (10.24%) [7]	1379.86 ± 163.69 (11.86%) [7]	1439.05 ± 180.10 (12.52%) [7]

[a] T_{max} is presented as Median (Minimum, Maximum)

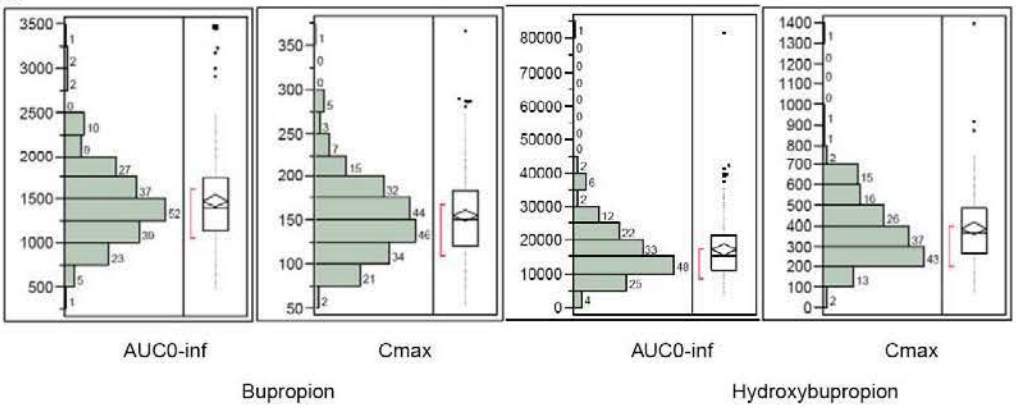
Abbreviations: AUC=area under the concentration-time curve from time zero until last quantifiable sample time (0-t) or extrapolated to infinity (0-∞), C_{max}=maximum plasma concentration; %CV=coefficient of variation; N=number of subjects; SD=standard deviation; $t_{1/2}$=apparent terminal elimination half-life; T_{max}=time to reach maximum plasma concentration.

Note: Subjects who vomited during the first 12 hours after dosing were excluded from the summary statistics.

Source: Report AA88068 Table 2.2.3

Discrete differences in CYP2B6 metabolic capacity evidenced by a bimodal or trimodal distribution might suggest a potential genetic contribution to bupropion exposure. As shown in the figure below, plasma bupropion and hydroxybupropion AUC_{0-12} and C_{max} data from pooled Phase 1 studies did not exhibit clear clustering of subjects with high exposures, with the exception of individual outliers. Additionally, Cmax and AUC0-12 at steady state varied evenly over the exposure range following multiple doses in study NB-236 (Day 30, following 7 days of 2 x naltrexone 8 mg/bupropion 90 mg SR tablets bid; n=17).

Figure 1. Bupropion and hydroxybupropion exposure distribution following single doses in pooled Phase 1 studies



It is noted that stereoselective assessment of bupropion hydroxylation may be a better probe of CYP2B6 activity (Kharasch, et al. J Clin Pharmacol 2008).

4 Summary and Conclusions

Bupropion and hydroxybupropion exposures do not appear to be excessively variable following single-doses. With the exception of outliers, bupropion and hydroxybupropion exposures did not appear to cluster at the high end of the range. Only one multiple-dose clinical pharmacology

study had dense PK sampling, limiting the ability to draw conclusions about the distribution of exposures at steady state in the target population. Marked race effects on bupropion PK were not apparent. Published pharmacogenetic and CYP2B6 inhibitor drug interaction studies suggest that genetic variation in CYP2B6 may account for a small proportion of the overall variability in bupropion exposure. Taken together, these findings suggest that CYP2B6 gene variants may explain a small proportion of the overall variability in bupropion or hydroxybupropion exposure. The applicant has collected DNA for Phase 3 trial participants should pharmacogenomic analyses be indicated on the basis of the efficacy and safety reviews.

5 Recommendations

The Genomics Group of the Office of Clinical Pharmacology has reviewed NDA 200,063 for naltrexone SR/bupropion SR in the management of obesity. The application is acceptable and no additional action is indicated at this time from the perspective of the Genomics Group.

5.1 Postmarketing commitments/requirements

Not applicable.

5.2. Label recommendations

Not applicable.

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Michael Pacanowski, Pharm.D., M.P.H.
Acting Team Leader, Genomics Group, OCP

4.4 OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	200063	Brand Name	Contrave®
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Buproprion, Naltrexone Combination
Medical Division	DMEP	Drug Class	Anti-obesity
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	Indicated for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification.
OCP Pharmacometrics Reviewer	Primary: Manoj Khurana Secondary: Christine Garnett	Dosage Form	Tri-layer Tablet
OCPB Team Leader	Sally Choe, Ph.D.	Dosing Regimen	Twice Daily
Date of Submission	February 23, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review	November 30, 2010	Sponsor	Orexigen Therapeutics
PDUFA Due Date	January 31, 2011	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		NB-206
multiple dose:	X	1		NB-236[#]
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		NB-232#, 233#, 234#
In-vivo effects of primary drug:	X			NB-236# (Counted under Multiple-Dose PK)
In-vitro:	X	2		0349-189-03, 0349-202-03
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	2		IR-PET, NB-222
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		NB-303#(One PopPK/PD Report)
Population Analyses -				
Data rich:	X			Phase 1 trials (included in PopPK analysis)
Data sparse:	X	1		NB-303# (One PopPK Report)
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	3		NB-230#, 228#, 229#
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		NB-236#, 239# (NB-236 counted under Multiple-dose PK)
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**15**		

Filability		
	"X" if yes	Comments
Is Application filable?	X	Comments to the Sponsor: a. Please provide raw data (SAS transport files) and the model codes for the two PKPD studies (IR-PET and NB-222). b. Please provide the NONMEM and WINBUGS Model Codes for the PopPK and PopPKPD analyses. You can follow the specifications mentioned in the Modeling and Simulations Plan Section 6 "Deliverables for Regulatory Submission" (page 325 of the Population Analysis Report by Metrum Dated Feb 9, 2010). In general, model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps.
Submission in Brief: See the details below.		Reviewer's Comments to project manager: • Please send a consult to IRT for review of the QTc analysis results. • From clinical pharmacology we have information requests for the sponsor to be sent in Day-74 letter as highlighted above

#Studies submitted with Analysis Data sets

Submission in Brief:

Sponsor, Orexigen Therapeutics has submitted a new drug application for CONTRAVE® (naltrexone HCL and bupropion HCL, **NB**) Extended-Release Tablets for the treatment of obesity and weight management. The active pharmaceutical ingredients in NB drug product are naltrexone HCL, a potent μ (mu) opioids antagonist, and bupropion HCL, a dopamine (DA) and norepinephrine (NE) reuptake inhibitor.

Each CONTRAVE tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and a more rapidly dissolving inert layer separating each drug. CONTRAVE will be available as two naltrexone dosage strength tablets:

- CONTRAVE 8/90, (naltrexone HCL 8 mg/bupropion HCL 90 mg) (b) (4) tablets
- CONTRAVE 4/90, (naltrexone HCL 4 mg/bupropion HCL 90 mg) (b) (4) tablets

The proposed recommended daily dose of NB is two 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion. NB dosing is escalated over a 3-week period until achieving the total daily maintenance dose of 32 mg naltrexone and 360 mg bupropion. Treatment initiation and escalation with NB 4/90 tablets may be considered. If well tolerated, patients using NB 4/90 tablets should switch to NB 8/90 tablets to have their daily dose increased to the recommended maintenance daily dose of 32 mg naltrexone and 360 mg bupropion (two NB

8/90 tablets twice daily) to maximize weight loss. However, patients initiated with NB 8/90 tablets that experience treatment intolerance during the escalation or early maintenance period can be switched to NB 4/90 tablets.

The NB (Contrave) clinical development program is composed of 23 trials, including 15 Phase 1, four Phase 2, and four pivotal Phase 3 studies. The 15 Phase 1 studies were conducted as part of the formulation development and/or clinical pharmacology programs.

A number of these studies were conducted to achieve multiple objectives (e.g., establishing both the effect of food on the pharmacokinetic (PK) profile of NB as well as investigating potential drug-drug interactions [DDIs]). Two of the Phase 1 trials (IR-PET and NB-222) were conducted to identify the extent and duration of opioid receptor occupancy associated with various doses of naltrexone; the results of these studies were important in the initial selection of naltrexone doses used in subsequent studies.

The studies compared the PK of investigational forms of immediate release (IR) and sustained release (SR) naltrexone (NB-221) and investigational forms of SR naltrexone and naltrexone SR/bupropion SR capsules (NB-225).

Trial (NB-230) compared the relative bioavailability (BA) of approved forms of naltrexone IR and bupropion SR tablets with the NB tablets used in Phase 3. Two studies (NB-228 and NB-229) allowed for an investigation of the relative BA of NB tablets manufactured at the site (b) (4) subsequently referred to as (b) (4) that supplied the majority of drug product used in Phase 3 and that will be used to manufacture commercial supplies versus the drug product made at two sites used during earlier stages of the development program (b) (4)

Results from four studies (NB-233, NB-236, NB-237, and NB-239) contributed to the evaluation of the effect of food on the PK of NB tablets, and four trials (NB-232, NB-233, NB-234, and NB-236) assessed the potential of PK DDIs between NB tablets and representative medications from pharmacological classes likely to be prescribed in parallel with NB (anti-hypertensive, anti-diabetic, and lipid lowering agents). Four studies (NB-231, NB-237, NB-238 and NB-239) examined the PK of NB combination monolayer tablets not advanced for approval in the present application.

Two Phase 2 studies (OT-101 and NB-201) were conducted to (1) demonstrate that the combination of naltrexone and bupropion produced greater weight loss than the individual fixed dose combinations of naltrexone and bupropion; and (2) to help determine which doses to evaluate in Phase 3. Although not the subject of this application, two open-label studies in special populations have been completed in overweight and obese subjects (nicotine dependent subjects [NB-401] and subjects who had major depression [NB-402]), and one double-blind study (NB-431) is ongoing in overweight or obese subjects in order to assess changes in blood-oxygen-level dependent (BOLD) signals in the brain through functional magnetic resonance imaging (fMRI) following treatment with NB or placebo in key brain areas associated with recognition of food cues and food-mediated reward.

The efficacy, safety and tolerability of NB were evaluated across four pivotal Phase 3 studies in obese subjects receiving customary diet and behavioral counseling (Studies NB-301 and NB-303), in obese subjects undergoing intensive lifestyle modification counseling (Study NB-302), and, as recommended by the current draft FDA guidance on the development of products for weight management (FDA 2007), in obese subjects with type 2 diabetes (Study NB-304). In each of

these studies, the efficacy of NB was evaluated using the FDA recommended co-primary endpoints of mean change from baseline in body weight at endpoint and the proportion of individuals who achieved a ≥5% reduction in body weight at endpoint. Although Studies NB-301, NB-302 and NB-303 enrolled a similar patient population (i.e., obese subjects with either uncomplicated obesity, or obese/overweight subjects 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 (naltrexone 16 mg/bupropion 360 mg [NB16] and naltrexone 32 mg/bupropion 360 mg [NB32]).

- Study NB-302 assessed the efficacy and safety of NB32 in a population of obese subjects undergoing an intensive behavioral modification program that included prescribed diet, exercise, and counseling.

- In Study NB-303, subjects who did not experience or maintain at least 5% weight loss between Weeks 28-44 of NB32 therapy were re-randomized to continue on NB32 or increase their daily dose to naltrexone 48 mg/bupropion 360 mg (NB48) to determine if the dose increase resulted in a therapeutic benefit.

- One of the four pivotal studies (Study NB-301) included a sub-study in which subjects underwent a body composition analysis and visceral fat measurement at baseline and after approximately 52 weeks of therapy, while another (Study NB-303) included a sub-study where blood pressure was measured over a 24-hour period at baseline, and after approximately 24 and 52 weeks of therapy.

Population pharmacokinetic analysis

Sponsor conducted population (PopPK) analysis and the goals of the analysis were to describe PK of NB tablets and to estimate the effects of covariates on the variability in PK parameters. Pharmacokinetic models were then implemented to predict exposure metrics for subjects enrolled in Study NB-303. Predicted pharmacokinetic data from this analysis and observed plasma trough concentrations were utilized for population PK/PD modeling. The eleven studies included in the PopPK data set were all well-controlled Phase 1 studies with strict inclusion/exclusion criteria for subject enrollment, which limited the range of covariate values. The effects of the covariates body size, age, race, and sex on the PK of naltrexone, bupropion and their metabolites were investigated.

Overall, sponsor claimed that the covariate analyses conducted in the PopPK analysis did not explain a significant portion of variability in NB and metabolite disposition. This may be due in part to poor estimation of some covariate effects, although those covariate effects that were well-defined were generally small in magnitude.

Exposure-Response Assessments

Exposure-response assessments conducted with PK data drawn from Phase 1 studies and from the Phase 3 study NB-303 (trough concentrations) were conducted to characterize (1) opioid receptor occupancy of naltrexone after oral administration; (2) the PK relationship to selected safety/tolerability endpoints and QT/QTc; and (3) the PK relationship to efficacy endpoints and effect of covariates on PD variability.

Phase 1 PK studies also calculated exposure parameters to a pharmacologically weighted composite of bupropion metabolites (PAWC). This composite represents an attempt to take into account the different potencies of biological activity in the metabolites and, therefore, present a more accurate overall picture of the potential biological consequences of exposure to bupropion and its active metabolites. A naltrexone PAWC consisting of a weighted composite of naltrexone and 6β-naltrexol was used for exposure response assessments.

In sponsor's analysis, the efficacy and tolerability exposure-response relationships suggested that higher exposure to naltrexone PAWC and bupropion PAWC was associated with the greatest observed weight loss. None of the covariates examined (sex, age, or race) explained a substantial portion of between-subject variability in subject response on efficacy endpoints. Exposure to NB was associated with nausea, but there was no clear relationship of nausea incidence to bupropion or naltrexone plasma trough concentrations. Similarly, there was no relationship of vital sign changes or the QT interval to plasma concentrations.

Clinical Pharmacology Review Questions:

- What is the dose-response, systemic exposure-response relationship for NB and their metabolites for efficacy?
    - What is the impact of covariates on exposure-response?
    - Does exposure-response information support the proposed dose?
- What is the systemic exposure-response relationship for NB and their metabolites for safety?
    - What is the concentration-QT relationship for NB and their metabolites with regards to safety?
    - Does exposure-safety information support the proposed dose?
- What is the effect of food on pharmacokinetics of NB and their metabolites?
    - Do the results warrant any dose adjustment?
    - Do the results support sponsor's proposed language?
    - Are analytical methods adequate?
- What is the effect of NB on other co-administered drugs and vice-versa?
    - Does the DDI result warrant for any dose adjustments for NB and the co-administered drugs?
    - Are analytical methods adequate?
- Are sponsor's assessments for specific populations appropriate and do they adequately support the proposed labeling language?
- What is the relative bioavailability of to-be-marketed formulation in comparison to the formulations used in the development phase?
    - Are analytical methods adequate?

Listing of Clinical Trials and Clinical Pharmacology Review Focus:

Clinical Pharmacology Program

- Total 23 trials – 15 Phase 1, four Phase 2 and four pivotal Phase 3 trials

TYPE	TRIAL	OBJECTIVE
PK/PD (Reports only)	**IR-PET & NB-222**	%RO using PET imaging – Selection of Naltrexone doses for the combination
PK (BA) (Reports & Raw Data)	**NB-230** N=27, BMI 19-40 Kg/m² **NB-232**	Relative BA of Phase 3/TBM NB formulation with approved Naltrexone IR and bupropion SR. Rel-BA of 4/90 versus 8/90
	NB-228 & 229 N=40 BMI 18-30/40 Kg/m²	Relative BA of Phase 3/TBM NB tablets (b) (4)
	NB- 236, 239 N=20, BMI ~18-40 Kg/m²	Food Effect
PK – DDI (Reports & Raw Data)	**NB-232, 233, 234 & 236** N=20, BMI ~18-40 Kg/m²	With Atorvastatin or Valsartan (232), Glyburide (233), Nifedipine or Lisinopril (234), Metoprolol (236)

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Clinical Pharmacology Program

- Total 23 trials – 15 Phase 1, four Phase 2 and four pivotal Phase 3 trials

TYPE	TRIAL	OBJECTIVE
PK (BA) (Reports & Raw Data)	**NB-230** N=27, BMI 19-40 Kg/m² **NB-232**	Relative BA of Phase 3/TBM NB formulation with approved Naltrexone IR and bupropion SR Rel-BA of 4/90 versus 8/90
	NB-228 & 229 N=40 BMI 18-30/40 Kg/m²	Relative BA of Phase 3/TBM NB tablets (b) (4) 229) and 229)
	NB- 236, 239 N~20, BMI ~18-40 Kg/m²	Food Effect
PK – DDI (Reports & Raw Data)	**NB-232, 233, 234 & 236** N~20, BMI ~18-40 Kg/m²	With Atorvastatin or Valsartan (232), Glyburide (233) Nifedipine or Lisinopril (234), Metoprolol (236)

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Efficacy/Safety Clinical Trials – Phase 2

Trial	Objective: Safety and Efficacy Comparison
POC: OT-101 ~48 week Primary 16 wk N=356 BMI 30-40 kg/m²	Fluoxetine 60 mg Capsule, Nal-SR 50 mg Caplet, Bup-SR 156 mg Tablet 1. Flu 60 mg QD + Nal-SR 50 mg QD 2. Flu 60 mg QD+ PBO 3. Bup-SR 150 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 Obese Nonsmoker
Dose Finding: NB-201 ~48 week Primary 24 wk N=419 BMI 30-40 kg/m²	Nal-SR 4, 8, and 12 mg tablet & Bup-SR 100 mg tablet 1. Bup-SR 200 + Nal-SR 24 mg BID 2. Bup-SR 200 + 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 Obese Nonsmoker

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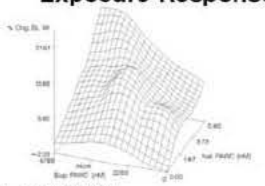
Efficacy/Safety Clinical Trials – Phase 3

Trial	Objective: Safety and Efficacy Comparison
NB-301 52 week N=1712 BMI 27-45 kg/m²	Nal-SR 4 mg / Bup-SR 90 mg (4/90) Tablet & Nal-SR 8 mg / Bup-SR 90 mg (8/90) Tablet, 4 wk titration 1. Nal-SR 4 mg/ Bup-SR 180 mg/BID 2. Nal-SR 8 mg/ Bup-SR 180 mg/BID or 3. Placebo/BID Obese/Overweight with controlled Hypertension and/or Dyslipidemia
NB-302 56 week N=756 BMI 27-45 kg/m²	Nal-SR 8 mg/ Bup-SR 90 mg (8/90) Tablet, with 4 wk titration 1. Nal-SR 16 mg/ Bup-SR 180 mg/BID or 2. Placebo/BID Obese/Overweight with controlled Hypertension and/or Dyslipidemia Nonsmoker
NB-303 56 week N=1496 BMI 27-45 kg/m²	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 with 4 wk titration 1. Nal-SR 16 mg/ Bup-SR 180 mg BID or 2. Placebo BID Re-randomization dose: 3. Nal-SR 24 mg/ Bup-SR 180 mg BID Obese/Overweight with controlled Hypertension and/or Dyslipidemia
NB-304 26 week N=505 BMI 27-45 kg/m²	Nal-SR 8 mg / Bup-SR 90 mg (8/90)Tablet with 4 wk titration 1. Nal-SR 16 mg/ Bup-SR 180 mg BID or 2. Placebo BID Obese/Overweight with Type 2 DM

Exposure-Response for Efficacy



Sponsor:

- Exposure-Response evident from the analysis for weight loss (efficacy)
- Covariate analysis - none of the covariate effects (race, age, sex) were estimated with sufficient precision, trial population limitations

- **Review Questions:**
  - What is the dose-response, systemic exposure-response relationship for NB and their metabolites for efficacy?
  - What is the impact of covariates on exposure-response?
  - Does exposure-response information support the proposed dose?
- **Filing Comments:**
  - **Information request for NONMEM / WinBUGS model codes**

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Exposure-Response for Safety

- **Sponsor:**
  - Nausea incidence unlikely to increase with ↑sed **N** or **B** plasma C_{trough} – could not evaluate Cmax-response relationship
  - Time-to-first nausea event dependent on **B** PAWC, but not to **N** PAWC exposures
  - Females more likely to experience nausea (0.460) vs. males (0.102)
  - Exposure-QT analysis from NB-228 and NB-303 trials and claimed no effect
- **Review Questions:**
  - What is the systemic exposure-response relationship for **NB** and their metabolites for safety?
  - What is the concentration-QT relationship for **NB** and their metabolites with regards to safety?
  - Does exposure-safety information support the proposed dose?
- **Filing Comments:**
  - **Information request for NONMEM / WinBUGS model codes**
  - **IRT Consult to be sent for review**

05/24/2010

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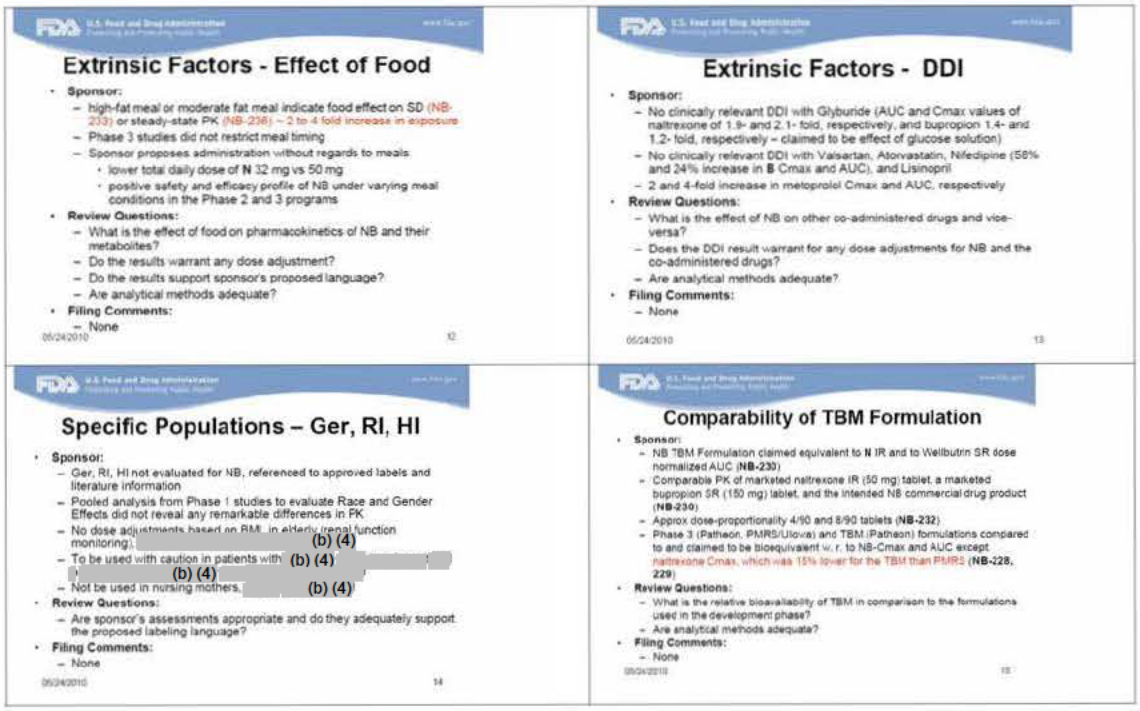

Extrinsic Factors - Effect of Food

- **Sponsor:**
  - high-fat meal or moderate fat meal indicate food effect on SD (NB-233) or steady-state PK (NB-236) – 2 to 4 fold increase in exposure
  - Phase 3 studies did not restrict meal timing
  - Sponsor proposes administration without regards to meals
    - lower total daily dose of **N** 32 mg vs 50 mg
    - positive safety and efficacy profile of NB under varying meal conditions in the Phase 2 and 3 programs
- **Review Questions:**
  - What is the effect of food on pharmacokinetics of NB and their metabolites?
  - Do the results warrant any dose adjustment?
  - Do the results support sponsor's proposed language?
  - Are analytical methods adequate?
- **Filing Comments:**
  - None

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Extrinsic Factors - DDI

- **Sponsor:**
  - No clinically relevant DDI with Glyburide (AUC and Cmax values of naltrexone of 1.9- and 2.1- fold, respectively, and bupropion 1.4- and 1.2- fold, respectively – claimed to be effect of glucose solution)
  - No clinically relevant DDI with Valsartan, Atorvastatin, Nifedipine (58% and 24% increase in **B** Cmax and AUC), and Lisinopril
  - 2 and 4-fold increase in metoprolol Cmax and AUC, respectively
- **Review Questions:**
  - What is the effect of NB on other co-administered drugs and vice-versa?
  - Does the DDI result warrant for any dose adjustments for NB and the co-administered drugs?
  - Are analytical methods adequate?
- **Filing Comments:**
  - None

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Specific Populations – Ger, RI, HI

- **Sponsor:**
  - Ger, RI, HI not evaluated for NB, referenced to approved labels and literature information
  - Pooled analysis from Phase 1 studies to evaluate Race and Gender Effects did not reveal any remarkable differences in PK
  - No dose adjustments based on BMI, in elderly (renal function monitoring), (b) (4)
  - To be used with caution in patients with (b) (4)
    (b) (4)
  - Not be used in nursing mothers. (b) (4)
- **Review Questions:**
  - Are sponsor's assessments appropriate and do they adequately support the proposed labeling language?
- **Filing Comments:**
  - None

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Comparability of TBM Formulation

- **Sponsor:**
  - NB TBM Formulation claimed equivalent to **N** IR and to Wellbutrin SR dose normalized AUC (**NB-230**)
  - Comparable PK of marketed naltrexone IR (50 mg) tablet, a marketed bupropion SR (150 mg) tablet, and the intended NB commercial drug product (**NB-230**)
  - Approx dose-proportionality 4/90 and 8/90 tablets (**NB-232**)
  - Phase 3 (Patheon, PMRS/Ulowa) and TBM (Patheon) formulations compared to and claimed to be bioequivalent w. r. to NB-Cmax and AUC except naltrexone Cmax, which was 15% lower for the TBM than PMRS (**NB-228, 229**)
- **Review Questions:**
  - What is the relative bioavailability of TBM in comparison to the formulations used in the development phase?
  - Are analytical methods adequate?
- **Filing Comments:**
  - None

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GRMP Filing Checklist:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 200063 **Applicant: Orexigen Therapeutics** **Stamp Date: 02/23/2010**

Drug Name: **Naltrexone/Bupropion**

NDA/BLA Type: Combination drug product (505(b)(2))

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	**X**		To be marketed formulation has been used in the pivotal clinical trials. BE trials compared Phase 2 and Phase 3 formulations.
2	Has the applicant provided metabolism and drug-drug interaction information?	**X**		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	**X**		Sponsor have not submitted control files for the population PK analysis and a request will be communicated in the filing letter
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			**NA**
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	**X**		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	**X**		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	**X**		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	**X**		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			**NA** Sponsor has requested a full waiver from conducting pediatric studies for patients from (b) (4) years of age.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			**NA**

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

MANOJ KHURANA	07/19/10
Reviewing Pharmacologist	Date
SALLY CHOE	07/19/10
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

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

/s/

MANOJ KHURANA
12/23/2010

MICHAEL A PACANOWSKI
12/23/2010

CHRISTINE E GARNETT
12/23/2010

SALLY Y CHOE
12/23/2010

CHANDRAHAS G G SAHAJWALLA
12/23/2010

ONDQA (Biopharmaceutics) Review

NDA:	200-063 (000)
Submission Date:	03/31/2010
Product:	Contrave®
Dosage Form:	Extended Release Tablets containing naltrexone HCl and bupropion HCl
Strength(s):	4/80 and 8/80 mg
Type of Submission:	Original NDA Submission
Sponsor:	Orexigen Therapeutics Inc.
Reviewer:	Tapash K. Ghosh, Ph.D.

Background: The sponsor submitted this NDA for CONTRAVE for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, to be used in conjunction with lifestyle modification. The proposed commercial drug product will be manufactured (under contract) by (b) (4) located in (b) (4) It is formulated as an extended release trilayer tablet containing two active ingredients: bupropion hydrochloride in one layer, an inert middle layer, and naltrexone hydrochloride in the other layer. The drug product manufacturing process consists of (b) (4) There are two drug product strengths, both with a single strength (90 mg) of bupropion hydrochloride per tablet, one with 4 mg naltrexone hydrochloride per tablet, and the other with 8 mg naltrexone hydrochloride per tablet. The tablets are film coated, using (b) (4) (b) (4) Opadry® II Blue (for the 8 mg naltrexone hydrochloride/ tablet product), (b) (4)

This review represents the evaluation of the sponsor's proposed in-vitro dissolution method and specification and the effect of alcohol (ethanol) upon in-vitro dissolution. For other aspects of the drug product quality review, see the CMC review. There is no biowaiver issue.

Recommendations:

3. *Based on the information provided, the sponsor's choice of the following in-vitro dissolution method is acceptable.*

Apparatus:	2 (Paddles)
Dissolution Media:	Water (degassed)
Media Volume:	900 mL
Temperature:	37 ± 0.5 °C
Shaft Speed:	50 RPM
Sampling Interval:	30 minutes, 1, 2, 3, 4, 6 hours
Sample Volume:	10 mL

4. *The sponsor's proposed dissolution specifications are not acceptable by the Agency. Based on the dissolution results from the stability batches, the following Table describes the Agency's recommendation with a side by side comparison to the sponsor's proposed specifications for both strengths (4/90 and 8/90 mg of naltrexone HCl and bupropion HCl respectively):*

Actives	**Time (Hr)**					
	0.5	1	2	3	4	6
	Sponsor's Proposed					
Naltrexone HCl	(b) (4)					
Bupropion HCl						
	Agency's Recommendation					
Naltrexone HCl	(b) (4)					
Bupropion HCl						

5. *According to 21 CFR 320.25 (f), to claim a product as "Controlled Release", the sponsor needs to conduct a study to demonstrate that the drug product's **steady-state performance** is equivalent to a currently marketed non-controlled release or controlled release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application. The sponsor did not conduct such a study. Therefore, the current submission did not fulfill all the requirements of the CFR for an "Extended Release" formulation.*

6. *The sponsor's evaluation of the effect of alcohol (ethanol) on the in-vitro dissolution of bupropion hydrochloride or naltrexone hydrochloride, as submitted in this NDA, is deficient as they did not investigate testing in 0.1 N HCl (pH 1.2) containing a range of alcohol concentrations to evaluate any potential for in-vivo dose dumping in presence of ethanol. The sponsor is requested to provide this data as soon as it is available for review.*

Tapash K. Ghosh, Ph. D.
Biopharmaceutics Primary Reviewer
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. _____

Drug Product Unit Composition:

4 mg/tablet Naltrexone Hydrochloride and 80 mg/tablet Bupropion Hydrochloride

Ingredient	Nominal Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet[1]	
(b) (4)				

8 mg/tablet Naltrexone Hydrochloride and 80 mg/tablet Bupropion Hydrochloride

Ingredient	Amount			Function
	mg/ tablet	wt% of layer	wt% of tablet[1]	
(b) (4)				
Bupropion Hydrochloride USP	90.0	(b) (4)	(b) (4)	Active ingredient
L-Cysteine Hydrochloride USP	(b) (4)			(b) (4)
Microcrystalline Cellulose (b) (4) NF				
Hydroxypropyl Cellulose (b) (4) NF				
Magnesium Stearate NF				
Layer total				
(b) (4)				
Microcrystalline Cellulose (b) (4) NF				(b) (4)
Lactose Anhydrous NF				
Crospovidone (b) (4) NF				
Magnesium Stearate NF				
FD&C Blue #2 Aluminum Lake				
(b) (4)				
Naltrexone Hydrochloride (b) (4) USP	8.0			Active ingredient
Microcrystalline Cellulose (b) (4) NF	(b) (4)			(b) (4)
Hypromellose USP (b) (4)				
Hydroxypropyl Cellulose (b) (4) NF				
Edetate Disodium USP				
Colloidal Silicon Dioxide NF				
Lactose Monohydrate (b) (4) NF				
Magnesium Stearate NF				
(b) (4)				
Opadry II Blue (b) (4)				(b) (4)
Overall total:	680		100	

Dissolution:

The goal of the development of the *in-vitro* dissolution method was to develop a method which allows simultaneous release of bupropion hydrochloride and naltrexone hydrochloride in the chosen dissolution condition including apparatus, speed medium and temperature. Also, an analytical method needed to be developed and validated to precisely quantitate the amount released for both ingredients using the same system set up. The sponsor conducted some initial experiments by varying some parameters of the various dissolution tests provided in the USP monograph for Bupropion Hydrochloride Extended-Release Tablets and Nalteroxne Hydrochloride Tablets. *In-vitro* dissolution methods for both the ingredients have some similarities in terms of chosen medium, apparatus and speed.

As a starting point for the selection of specified sampling times and acceptance criteria, the sponsor compared the overall release/stability dissolution results generated throughout development to the various dissolution tests provided in the USP monograph for Bupropion Hydrochloride Extended-Release Tablets. From consideration of the methodology, intended dosing regimen and batch data, the best fit was determined to be (b) (4) The following section describes the dissolution parameters, the procedure and the analytical method proposed by the sponsor.

Dissolution Procedure

(b) (4)

Dissolution Parameters

Apparatus:	2 (Paddles)
Dissolution Media:	Water (degassed)
Media Volume:	900 mL
Temperature:	37 ± 0.5 °C
Shaft Speed:	50 RPM
Sampling Interval:	30 minutes, 1, 2, 3, 4, 6 hours
Sample Volume:	10 mL

(b) (4)

Analytical (HPLC) Parameters

The following HPLC method was developed and validated to simultaneously determine amount of bupropion hydrochloride and naltrexone hydrochloride using (b) (4)

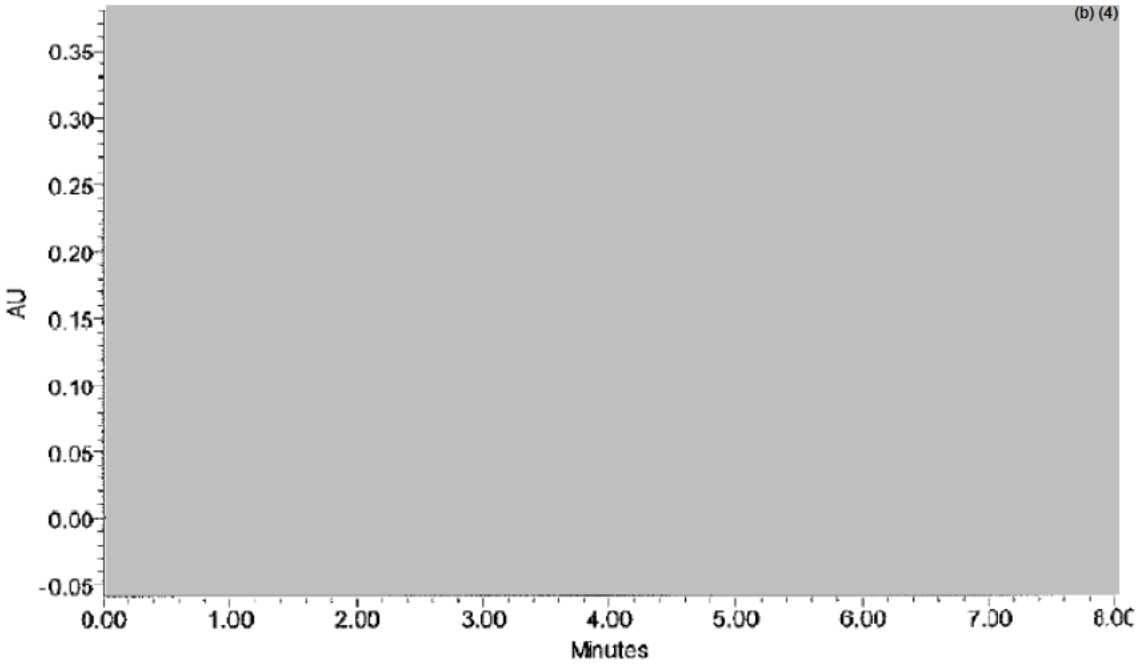
(b) (4)

Analytical Column:
Column Temperature
Mobile Phase(s):

Flow Rate:
Injection Volume:
Needle Wash:
Wavelength:

Run Time:

(b) (4)



Discriminating Power: (b) (4)

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Summary Data: A summary of the above results is presented in the following Table:

Strength	Batch #	Dissolution (% LC Dissolved in Hr.)															
4/90		Bupripion HCl [Avg]										Naltrexone HCl [Avg]					
		0.5	1	2	3	4	6					0.5	1	2	3	4	6
	C9F2069	(b) (4)															
	C9F2070																
	C9F2071																
	Average																
	SD																
	%RSD																
Sponsor's Proposed Spec																	
Agency's Proposed Spec																	
8/90		Bupripion HCl [Avg]										Naltrexone HCl [Avg]					
	C9F2072	(b) (4)															
	C9F2073																
	C9F2074																
	Average																
	SD																
	%RSD																
Sponsor's Proposed Spec																	

(b) (4)

(b) (4)

(b) (4)

Based on the dissolution results from the stability batches, the following Table describes the Agency's recommendation with a side by side comparison to the sponsor's proposed specifications for both strengths (4/90 and 8/90 mg of naltrexone HCl and bupropion HCl respectively):

Actives	Time (Hr)					
	0.5	1	2	3	4	6
	Sponsor's Proposed					
Naltrexone HCl	(b) (4)					
Bupropion HCl						
	Agency's Recommendation					
Naltrexone HCl	(b) (4)					
Bupropion HCl						

Discussion:

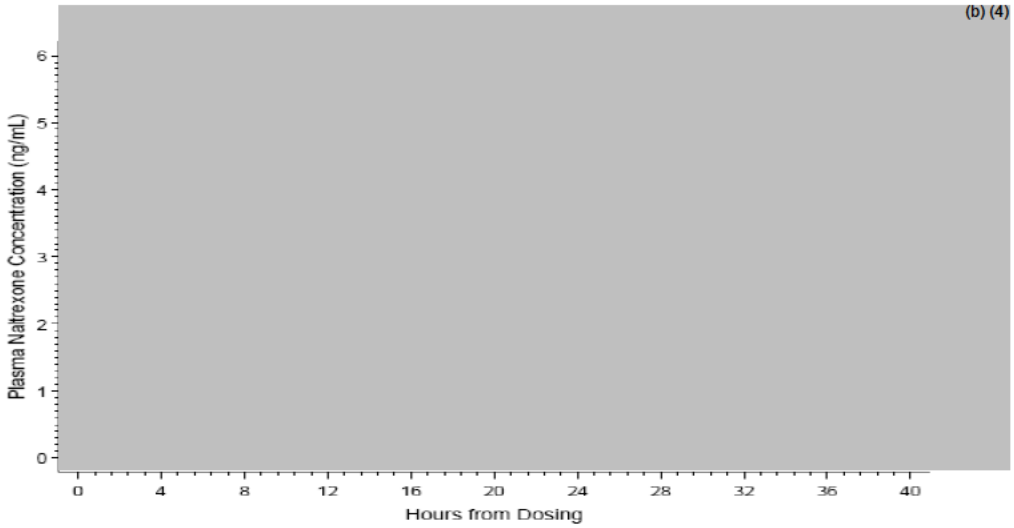
The sponsor claimed the proposed product as an "extended-release" tablet. However, both the ingredients are released more than (b) (4) % by about 3 hours in the chosen dissolution medium. However, to evaluate the sponsor's claim of the proposed product as "Extended Release", the following information was considered:

1. A Phase 1, Open-Label, Randomized, Single-Dose, Three-Way Crossover Study was conducted to Assess the Relative Bioavailability of Naltrexone SR/Bupropion SR Combination Trilayer Tablet to Commercially Available Tablet Formulations of Naltrexone IR and Bupropion SR in Healthy Adult Subjects(NP-230). The 3 study treatments (A, B, and C) were as follows:

A = Two Naltrexone SR 8 mg/Bupropion SR 90 mg Trilayer Tablets (Test)
B = One Naltrexone IR 50 mg Tablet (Reference 1)
C = One Bupropion SR 150 mg Tablet (Reference 2)

The following Tables and Figures describe the PK profiles/parameters of proposed product and the reference immediate release (IR) products.

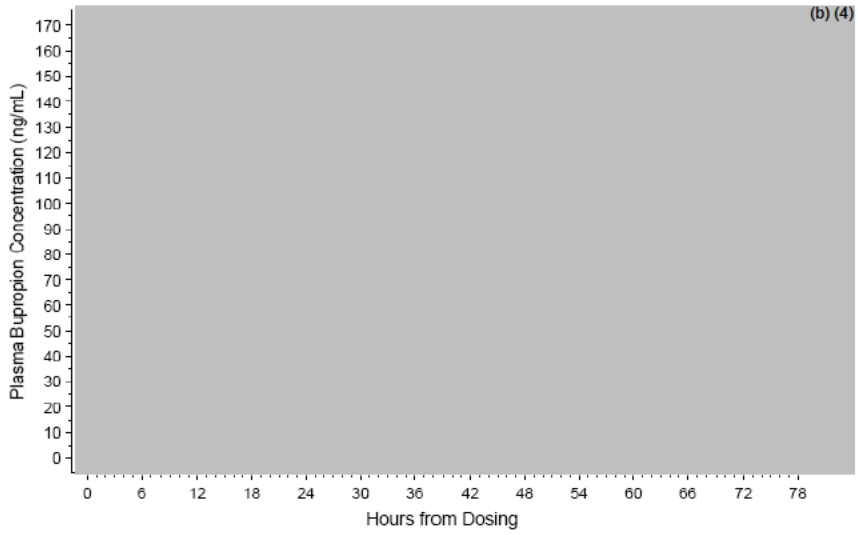
Figure 11-1 Mean Plasma Naltrexone Concentrations Versus Time (N = 27)



Arithmetic Mean ± SD Plasma Naltrexone Pharmacokinetic Parameters

Analyte	Pharmacokinetic Parameters	Nal SR/Bup SR Mean ± SD (N)	Nal IR Mean ± SD (N)
Plasma Naltrexone	C_{max} (ng/mL)	1.36 ± 0.914 (26)	7.55 ± 4.62 (24)
	T_{max} (hr)	2.00 (0.50, 5.99) (26)	1.00 (0.50, 3.00) (24)
	$t_{1/2}$ (hr)	5.33 ± 2.26 (25)	7.37 ± 2.58 (22)
	AUC_{0-t} (ng*hr/mL)	8.02 ± 4.49 (26)	25.93 ± 12.40 (24)
	$AUC_{0-\infty}$ (ng*hr/mL)	8.40 ± 4.57 (25)	27.25 ± 12.60 (22)

Figure 11-3 Mean Plasma Bupropion Concentrations Versus Time (N = 27)



Arithmetic Mean ± SD Plasma Bupropion Pharmacokinetic Parameters

Analyte	Pharmacokinetic Parameters	Nal SR/Bup SR Mean ± SD (N)	Bup SR Mean ± SD (N)
Plasma Bupropion	C_{max} (ng/mL)	168 ± 53.4 (26)	172 ± 57.9 (26)
	T_{max} (hr)	3.00 (1.00, 6.11) (26)	3.00 (1.00, 4.07) (26)
	$t_{1/2}$ (hr)	21.08 ± 5.61 (26)	22.23 ± 7.08 (26)
	AUC_{0-t} (ng*hr/mL)	1544.93 ± 379.29 (26)	1427.15 ± 386.75 (26)
	$AUC_{0-\infty}$ (ng*hr/mL)	1606.73 ± 393.53 (26)	1492.20 ± 406.06 (26)

Comments: *According to 21 CFR 320.25 (f), to claim a product as "Controlled Release", the sponsor needs to conduct a study to demonstrate that the drug product's* ***steady-state performance*** *is equivalent to a currently marketed non-controlled release or controlled release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application. The sponsor did not conduct such a study. Therefore, the current submission did not fulfill all the requirements of the CFR for an "Extended Release" formulation.*

Overall Comments:

1. *The sponsor conducted some initial experiments by varying some parameters of the various dissolution tests provided in the USP monograph for Bupropion Hydrochloride Extended-Release Tablets and Naltrexone Hydrochloride Tablets. Eventually, the sponsor adopted a method very similar to* (b) (4) *for Bupropion HCl extended release tablets with minor differences. Based on the information provided, the sponsor's choice of method is acceptable. However, during optimization of the dissolution method, the sponsor should have conducted studies with the* (b) (4)

2. *The sponsor's proposed dissolution specifications are not acceptable by the Agency. Based on the dissolution results from the stability batches, the following Table describes the Agency's recommendation with a side by side comparison to the sponsor's proposed specifications for both strengths (4/90 and 8/90 mg of naltrexone HCl and bupropion HCl respectively):*

Actives	**Time (Hr)**					
	0.5	1	2	3	4	6
	Sponsor's Proposed					
Naltrexone HCl	(b) (4)					
Bupropion HCl						
	Agency's Recommendation					
Naltrexone HCl	(b) (4)					
Bupropion HCl						

3. *According to 21 CFR 320.25 (f), to claim a product as "Controlled Release", the sponsor needs to conduct a study to demonstrate that the drug product's* ***steady-state performance*** *is equivalent to a currently marketed non-controlled release or controlled release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application. The sponsor did not conduct such a study. Therefore, the current submission did not fulfill all the requirements of the CFR for an "Extended Release" formulation.*

Effect of Alcohol (ethanol) upon *in-vitro* Dissolution

In order to address the possibility of dose dumping of bupropion hydrochloride when the extended release drug product is taken with alcohol, dissolution testing using 0-40 volume % ethanol in the dissolution medium was performed. Drug product registration batches C9F2069 (90 mg bupropion hydrochloride and 4 mg naltrexone hydrochloride per tablet) and C9F2072 (90 mg bupropion hydrochloride and 8 mg naltrexone hydrochloride per tablet) were used for this study, with bupropion hydrochloride and naltrexone hydrochloride data from twelve (12) units from each dissolution run collected every 15 minutes for two (2) hours. Test was performed using the proposed commercial drug product release/stability testing (900 mL water, USP Apparatus 2 at 50 rpm, sinker used). Control experiments were performed to confirm the specificity and accuracy of the dissolution test HPLC parameters in the presence of alcohol.

Results: The following figures describe the results of this alcohol interaction study:

Figure 1: *Bupropion Hydrochloride Dissolution for Drug Product Batch C9F2069 (90 mg Bupropion Hydrochloride/4 mg Naltrexone Hydrochloride per Tablet) in Hydroalcoholic Media*

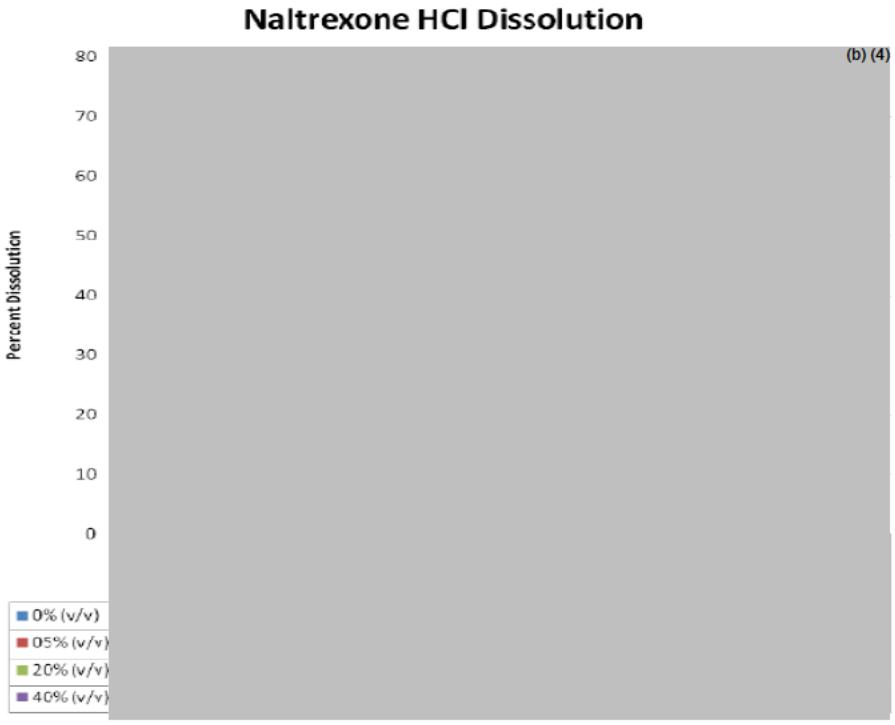


Figure 2: *Naltrexone Hydrochloride Dissolution for Drug Product Batch C9F2069 (90 mg Bupropion Hydrochloride/4 mg Naltrexone Hydrochloride per Tablet) in Hydroalcoholic Media*

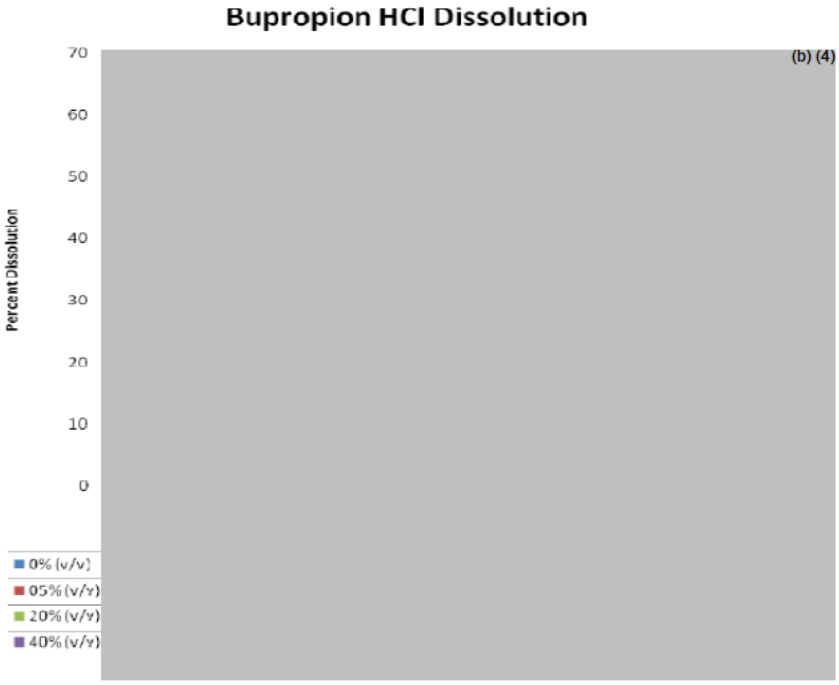


Figure 3: *Bupropion Hydrochloride Dissolution for Drug Product Batch C9F2072 (90 mg Bupropion Hydrochloride/8 mg Naltrexone Hydrochloride per Tablet) in Hydroalcoholic Media*

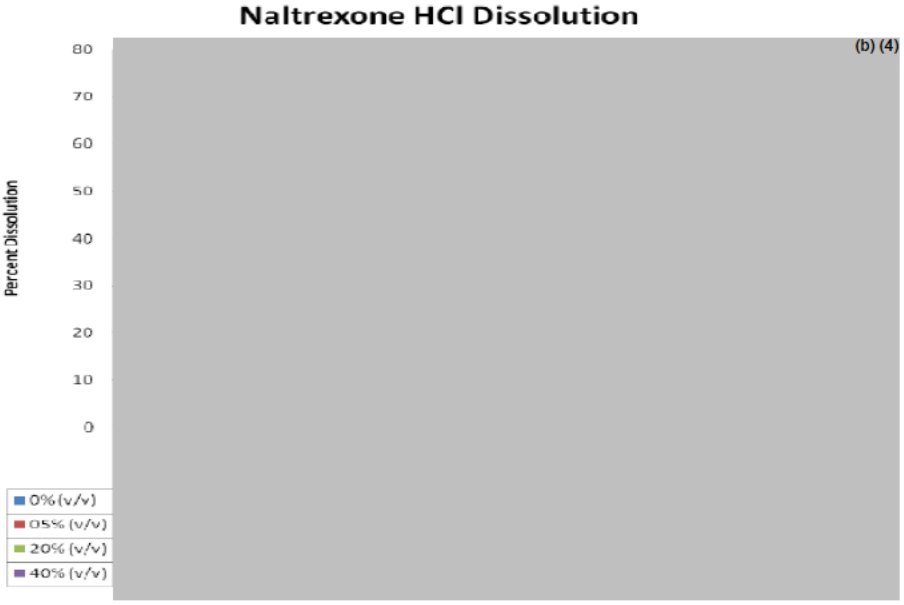


Figure 4: *Naltrexone Hydrochloride Dissolution for Drug Product Batch C9F2072 (90 mg Bupropion Hydrochloride/8 mg Naltrexone Hydrochloride per Tablet) in Hydroalcoholic Media*

Discussion: The above results demonstrates that neither batch exhibited dose dumping of bupropion hydrochloride or naltrexone hydrochloride in the presence of alcoholic dissolution media. Rather, it revealed that dissolution of both bupropion hydrochloride or naltrexone hydrochloride slowed down significantly in the alcoholic medium. The sponsor did not provide any explanation for this slowing of dissolution in presence of alcohol.

However, the sponsor's evaluation of the effect of alcohol (ethanol) on the in-vitro dissolution of bupropion hydrochloride or naltrexone hydrochloride, as submitted in this NDA, is not acceptable. As the optimal dissolution medium is not 0.1 N HCl, dissolution testing in 0.1 N HCl (pH 1.2) containing a range of alcohol concentrations is necessary for the Agency to evaluate any potential for *in-vivo* dose dumping in presence of ethanol.

Conclusion: *The sponsor's evaluation of the effect of alcohol (ethanol) on the in-vitro dissolution of bupropion hydrochloride or naltrexone hydrochloride, as submitted in this NDA, is deficient as they did not investigate testing in 0.1 N HCl (pH 1.2) containing a range of alcohol concentrations to evaluate any potential for in-vivo dose dumping in presence of ethanol. The sponsor is requested to provide this data as soon as it is available for review.*

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

/s/

TAPASH K GHOSH
12/21/2010

PATRICK J MARROUM
12/21/2010

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	200063	Brand Name	Contrave®
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Buproprion, Naltrexone Combination
Medical Division	DMEP	Drug Class	Anti-obesity
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	Indicated for the treatment of obesity and weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with lifestyle modification.
OCP Pharmacometrics Reviewer	Primary: Manoj Khurana Secondary: Christine Garnett	Dosage Form	Tri-layer Tablet
OCPB Team Leader	Sally Choe, Ph.D.	Dosing Regimen	Twice Daily
Date of Submission	February 23, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review	November 30, 2010	Sponsor	Orexigen Therapeutics
PDUFA Due Date	January 31, 2011	Priority Classification	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	1		NB-206
multiple dose:	**X**	1		NB-236[#]
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	3		NB-232#, 233#, 234#
In-vivo effects of primary drug:	**X**			NB-236# (Counted under Multiple-Dose PK)
In-vitro:	**X**	2		0349-189-03, 0349-202-03
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	**X**	2		IR-PET, NB-222
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	1		NB-303#(One PopPK/PD Report)
Population Analyses -				
Data rich:	**X**			Phase 1 trials (included in PopPK analysis)
Data sparse:	**X**	1		NB-303# (One PopPK Report)
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	3		NB-230#, 228#, 229#
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	1		NB-236#, 239# (NB-236 counted under Multiple-dose PK)
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**15**		

Filability		
	"X" if yes	**Comments**
Is Application filable?	**X**	**Comments to the Sponsor:** **a. Please provide raw data (SAS transport files) and the model codes for the two PKPD studies (IR-PET and NB-222).** **b. Please provide the NONMEM and WINBUGS Model Codes for the PopPK and PopPKPD analyses. You can follow the specifications mentioned in the Modeling and Simulations Plan Section 6 "Deliverables for Regulatory Submission" (page 325 of the Population Analysis Report by Metrum Dated Feb 9, 2010). In general, model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps.**
Submission in Brief: See the details below.	**Reviewer's Comments to project manager:** • **Please send a consult to IRT for review of the QTc analysis results.** • **From clinical pharmacology we have information requests for the sponsor to be sent in Day-74 letter as highlighted above**	

#Studies submitted with Analysis Data sets

Submission in Brief:

Sponsor, Orexigen Therapeutics has submitted a new drug application for CONTRAVE® (naltrexone HCL and bupropion HCL, **NB**) Extended-Release Tablets for the treatment of obesity and weight management. The active pharmaceutical ingredients in NB drug product are naltrexone HCL, a potent μ (mu) opioids antagonist, and bupropion HCL, a dopamine (DA) and norepinephrine (NE) reuptake inhibitor.

Each CONTRAVE tablet has a trilayer core that is composed of two drug layers containing the drug and excipients, and a more rapidly dissolving inert layer separating each drug. CONTRAVE will be available as two naltrexone dosage strength tablets:

- CONTRAVE 8/90, (naltrexone HCL 8 mg/bupropion HCL 90 mg) (b) (4) tablets
- CONTRAVE 4/90, (naltrexone HCL 4 mg/bupropion HCL 90 mg) (b) (4) tablets

The proposed recommended daily dose of NB is two 8/90 tablets taken twice daily for a total dose of 32 mg naltrexone/360 mg bupropion. NB dosing is escalated over a 3-week period until achieving the total daily maintenance dose of 32 mg naltrexone and 360 mg bupropion. Treatment initiation and escalation with NB 4/90 tablets may be considered. If well tolerated, patients using NB 4/90 tablets should switch to NB 8/90 tablets to have their daily dose increased to the recommended maintenance daily dose of 32 mg naltrexone and 360 mg bupropion (two NB

8/90 tablets twice daily) to maximize weight loss. However, patients initiated with NB 8/90 tablets that experience treatment intolerance during the escalation or early maintenance period can be switched to NB 4/90 tablets.

The NB (Contrave) clinical development program is composed of 23 trials, including 15 Phase 1, four Phase 2, and four pivotal Phase 3 studies. The 15 Phase 1 studies were conducted as part of the formulation development and/or clinical pharmacology programs.

A number of these studies were conducted to achieve multiple objectives (e.g., establishing both the effect of food on the pharmacokinetic (PK) profile of NB as well as investigating potential drug-drug interactions [DDIs]). Two of the Phase 1 trials (IR-PET and NB-222) were conducted to identify the extent and duration of opioid receptor occupancy associated with various doses of naltrexone; the results of these studies were important in the initial selection of naltrexone doses used in subsequent studies.

The studies compared the PK of investigational forms of immediate release (IR) and sustained release (SR) naltrexone (NB-221) and investigational forms of SR naltrexone and naltrexone SR/bupropion SR capsules (NB-225).

Trial (NB-230) compared the relative bioavailability (BA) of approved forms of naltrexone IR and bupropion SR tablets with the NB tablets used in Phase 3. Two studies (NB-228 and NB-229) allowed for an investigation of the relative BA of NB tablets manufactured at the site (b) (4) (b) (4) subsequently referred to as (b) (4) that supplied the majority of drug product used in Phase 3 and that will be used to manufacture commercial supplies versus the drug product made at two sites used during earlier stages of the development program (b) (4)

Results from four studies (NB-233, NB-236, NB-237, and NB-239) contributed to the evaluation of the effect of food on the PK of NB tablets, and four trials (NB-232, NB-233, NB-234, and NB-236) assessed the potential of PK DDIs between NB tablets and representative medications from pharmacological classes likely to be prescribed in parallel with NB (anti-hypertensive, anti-diabetic, and lipid lowering agents). Four studies (NB-231, NB-237, NB-238 and NB-239) examined the PK of NB combination monolayer tablets not advanced for approval in the present application.

Two Phase 2 studies (OT-101 and NB-201) were conducted to (1) demonstrate that the combination of naltrexone and bupropion produced greater weight loss than the individual fixed dose combinations of naltrexone and bupropion; and (2) to help determine which doses to evaluate in Phase 3. Although not the subject of this application, two open-label studies in special populations have been completed in overweight and obese subjects (nicotine dependent subjects [NB-401] and subjects who had major depression [NB-402]), and one double-blind study (NB-431) is ongoing in overweight or obese subjects in order to assess changes in blood-oxygen-level dependent (BOLD) signals in the brain through functional magnetic resonance imaging (fMRI) following treatment with NB or placebo in key brain areas associated with recognition of food cues and food-mediated reward.

The efficacy, safety and tolerability of NB were evaluated across four pivotal Phase 3 studies in obese subjects receiving customary diet and behavioral counseling (Studies NB-301 and NB-303), in obese subjects undergoing intensive lifestyle modification counseling (Study NB-302), and, as recommended by the current draft FDA guidance on the development of products for weight management (FDA 2007), in obese subjects with type 2 diabetes (Study NB-304). In each of

these studies, the efficacy of NB was evaluated using the FDA recommended co-primary endpoints of mean change from baseline in body weight at endpoint and the proportion of individuals who achieved a ≥5% reduction in body weight at endpoint. Although Studies NB-301, NB-302 and NB-303 enrolled a similar patient population (i.e., obese subjects with either uncomplicated obesity, or obese/overweight subjects 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 (naltrexone 16 mg/bupropion 360 mg [NB16] and naltrexone 32 mg/bupropion 360 mg [NB32]).

- Study NB-302 assessed the efficacy and safety of NB32 in a population of obese subjects undergoing an intensive behavioral modification program that included prescribed diet, exercise, and counseling.

- In Study NB-303, subjects who did not experience or maintain at least 5% weight loss between Weeks 28-44 of NB32 therapy were re-randomized to continue on NB32 or increase their daily dose to naltrexone 48 mg/bupropion 360 mg (NB48) to determine if the dose increase resulted in a therapeutic benefit.

- One of the four pivotal studies (Study NB-301) included a sub-study in which subjects underwent a body composition analysis and visceral fat measurement at baseline and after approximately 52 weeks of therapy, while another (Study NB-303) included a sub-study where blood pressure was measured over a 24-hour period at baseline, and after approximately 24 and 52 weeks of therapy.

Population pharmacokinetic analysis

Sponsor conducted population (PopPK) analysis and the goals of the analysis were to describe PK of NB tablets and to estimate the effects of covariates on the variability in PK parameters. Pharmacokinetic models were then implemented to predict exposure metrics for subjects enrolled in Study NB-303. Predicted pharmacokinetic data from this analysis and observed plasma trough concentrations were utilized for population PK/PD modeling. The eleven studies included in the PopPK data set were all well-controlled Phase 1 studies with strict inclusion/exclusion criteria for subject enrollment, which limited the range of covariate values. The effects of the covariates body size, age, race, and sex on the PK of naltrexone, bupropion and their metabolites were investigated.

Overall, sponsor claimed that the covariate analyses conducted in the PopPK analysis did not explain a significant portion of variability in NB and metabolite disposition. This may be due in part to poor estimation of some covariate effects, although those covariate effects that were well-defined were generally small in magnitude.

Exposure-Response Assessments

Exposure-response assessments conducted with PK data drawn from Phase 1 studies and from the Phase 3 study NB-303 (trough concentrations) were conducted to characterize (1) opioid receptor occupancy of naltrexone after oral administration; (2) the PK relationship to selected safety/tolerability endpoints and QT/QTc; and (3) the PK relationship to efficacy endpoints and effect of covariates on PD variability.

Phase 1 PK studies also calculated exposure parameters to a pharmacologically weighted composite of bupropion metabolites (PAWC). This composite represents an attempt to take into account the different potencies of biological activity in the metabolites and, therefore, present a more accurate overall picture of the potential biological consequences of exposure to bupropion and its active metabolites. A naltrexone PAWC consisting of a weighted composite of naltrexone and 6β-naltrexol was used for exposure response assessments.

In sponsor's analysis, the efficacy and tolerability exposure-response relationships suggested that higher exposure to naltrexone PAWC and bupropion PAWC was associated with the greatest observed weight loss. None of the covariates examined (sex, age, or race) explained a substantial portion of between-subject variability in subject response on efficacy endpoints. Exposure to NB was associated with nausea, but there was no clear relationship of nausea incidence to bupropion or naltrexone plasma trough concentrations. Similarly, there was no relationship of vital sign changes or the QT interval to plasma concentrations.

Clinical Pharmacology Review Questions:

- What is the dose-response, systemic exposure-response relationship for NB and their metabolites for efficacy?
    - What is the impact of covariates on exposure-response?
    - Does exposure-response information support the proposed dose?
- What is the systemic exposure-response relationship for NB and their metabolites for safety?
    - What is the concentration-QT relationship for NB and their metabolites with regards to safety?
    - Does exposure-safety information support the proposed dose?
- What is the effect of food on pharmacokinetics of NB and their metabolites?
    - Do the results warrant any dose adjustment?
    - Do the results support sponsor's proposed language?
    - Are analytical methods adequate?
- What is the effect of NB on other co-administered drugs and vice-versa?
    - Does the DDI result warrant for any dose adjustments for NB and the co-administered drugs?
    - Are analytical methods adequate?
- Are sponsor's assessments for specific populations appropriate and do they adequately support the proposed labeling language?
- What is the relative bioavailability of to-be-marketed formulation in comparison to the formulations used in the development phase?
    - Are analytical methods adequate?

Listing of Clinical Trials and Clinical Pharmacology Review Focus:

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Clinical Pharmacology Program

- Total 23 trials – 15 Phase 1, four Phase 2 and four pivotal Phase 3 trials

TYPE	TRIAL	OBJECTIVE
PK/PD **(Reports only)**	**IR-PET & NB-222**	%RO using PET imaging – Selection of Naltrexone doses for the combination
PK (BA) **(Reports & Raw Data)**	**NB-230** N=27, BMI 19-40 Kg/m² **NB-232**	Relative BA of Phase 3/TBM NB formulation wi h approved Naltrexone IR and bupropion SR. Rel-BA of 4/90 versus 8/90
	NB-228 & 229 N=40 BMI 18-30/40 Kg/m²	Relative BA of Phase 3/TBM NB tablets (b) (4)
	NB- 236, 239 N~20, BMI ~18-40 Kg/m²	Food Effect
PK – DDI **(Reports & Raw Data)**	**NB-232, 233, 234 & 236** N~20, BMI ~18-40 Kg/m²	With Atorvastatin or Valsartan (232), Glyburide (233), Nifedipine or Lisinopril (234), Metoprolol (236)

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Clinical Pharmacology Program

- Total 23 trials – 15 Phase 1, four Phase 2 and four pivotal Phase 3 trials

TYPE	TRIAL	OBJECTIVE
PK (BA) **(Reports & Raw Data)**	**NB-230** N=27, BMI 19-40 Kg/m² **NB-232**	Relative BA of Phase 3/TBM NB formulation with approved Naltrexone IR and bupropion SR. Rel-BA of 4/90 versus 8/90
	NB-228 & 229 N=40 BMI 18-30/40 Kg/m²	Relative BA of Phase 3/TBM NB tablets (b) (4)
	NB- 236, 239 N~20, BMI ~18-40 Kg/m²	Food Effect
PK – DDI **(Reports & Raw Data)**	**NB-232, 233, 234 & 236** N~20, BMI ~18-40 Kg/m²	With Atorvastatin or Valsartan (232), Glyburide (233), Nifedipine or Lisinopril (234), Metoprolol (236)

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Efficacy/Safety Clinical Trials – Phase 2

Trial	Objective: Safety and Efficacy Comparison
POC: **OT-101** ~48 week Primary 16 wk N=358 BMI 30-40 kg/m²	Fluoxetine 60 mg Capsule, Nal-SR 50 mg Caplet, Bup-SR150 mg Tablet 1. Flu 60 mg QD + Nal-SR 50 mg QD 2. Flu 60 mg QD+ PBO 3. Bup-SR 150 mg B D + Nal-SR 50 mg QD 4. Bup-SR 150 mg B D + PBO QD 5. PBO B D + Nal-SR 50 mg QD 6. PBO B D + PBO QD Obese Nonsmoker
Dose Finding: **NB-201** ~48 week Primary 24 wk N=419 BMI 30-40 kg/m²	Nal-SR 4, 8, and 12 mg tablet & Bup-SR 100 mg tablet 1. Bup-SR 200 + Nal-SR 24 mg B D 2. Bup-SR 200 + Nal-SR 8 mg BID 3. Bup-SR 200 + PBO/ B D 4. PBO + Nal-SR 24 mg/ B D 5. PBO + PBO/ BID 6. Bup-SR 200 mg +Nal-SR 16 mg/B D Obese Nonsmoker

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Efficacy/Safety Clinical Trials – Phase 3

Trial	Objective: Safety and Efficacy Comparison
NB-301 57 week N=1742 BMI 27-45 kg/m²	Nal-SR 4 mg / Bup-SR 90 mg (4/90) Tablet & Nal-SR 8 mg / Bup-SR 90 mg (8/90) Tablet, 4 wk titration **1.** Nal-SR 4 mg/ Bup-SR 180 mg/BID **2.** Nal-SR 8 mg/ Bup-SR 180 mg/BID or **3.** Placebo/BID Obese/Overweight with controlled Hypertension and/or Dyslipidemia
NB-302 56 week N=793 BMI 27-45 kg/m²	Nal-SR 8 mg/ Bup-SR 90 mg (8/90) Tablet, with 4 wk titration 1. Nal-SR 16 mg/ Bup-SR 180 mg/BID or 2. Placebo/BID Obese/Overweight with controlled Hypertension and/or Dyslipidemia Nonsmoker
NB-303 56 week N=1496 BMI 27-45 kg/m²	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 with 4 wk titration **1.** Nal-SR 16 mg/ Bup-SR 180 mg BID or **2.** Placebo BID Re-randomization dose: **3.** Nal-SR 24 mg/ Bup-SR 180 mg BID Obese/Overweight with controlled Hypertension and/or Dyslipidemia
NB-304 56 week N=505 BMI 27-45 kg/m²	Nal-SR 8 mg / Bup-SR 90 mg (8/90)Tablet with 4 wk titration **1.** Nal-SR 16 mg/ Bup-SR 180 mg BID or **2.** Placebo BID Obese/Overweight with Type 2 DM

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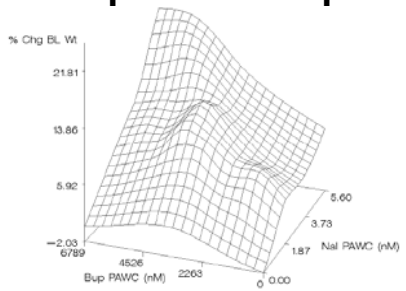
Exposure-Response for Efficacy



Sponsor:

- Exposure-Response evident from the analysis for weight loss (efficacy)
- Covariate analysis - none of the covariate effects (race, age, sex) were estimated with sufficient precision, trial population limitations

- **Review Questions:**
  - What is the dose-response, systemic exposure-response relationship for NB and their metabolites for efficacy?
  - What is the impact of covariates on exposure-response?
  - Does exposure-response information support the proposed dose?
- **Filing Comments:**
  - **Information request for NONMEM / WinBUGS model codes**

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Exposure-Response for Safety

- **Sponsor:**
  - Nausea incidence unlikely to increase with ↑sed **N** or **B** plasma C_{trough} – could not evaluate Cmax-response relationship
  - Time-to-first nausea event dependent on **B** PAWC, but not to **N** PAWC exposures
  - Females more likely to experience nausea (0.460) vs. males (0.102)
  - Exposure-QT analysis from NB-228 and NB-303 trials and claimed no effect
- **Review Questions:**
  - What is the systemic exposure-response relationship for **NB** and their metabolites for safety?
  - What is the concentration-QT relationship for **NB** and their metabolites with regards to safety?
  - Does exposure-safety information support the proposed dose?
- **Filing Comments:**
  - **Information request for NONMEM / WinBUGS model codes**
  - **IRT Consult to be sent for review**

05/24/2010

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Extrinsic Factors - Effect of Food

- **Sponsor:**
  - high-fat meal or moderate fat meal indicate food effect on SD (NB-233) or steady-state PK (NB-236) ~ 2 to 4 fold increase in exposure
  - Phase 3 studies did not restrict meal timing
  - Sponsor proposes administration without regards to meals
    - lower total daily dose of **N** 32 mg vs 50 mg
    - positive safety and efficacy profile of NB under varying meal conditions in the Phase 2 and 3 programs
- **Review Questions:**
  - What is the effect of food on pharmacokinetics of NB and their metabolites?
  - Do the results warrant any dose adjustment?
  - Do the results support sponsor's proposed language?
  - Are analytical methods adequate?
- **Filing Comments:**
  - None

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Extrinsic Factors - DDI

- **Sponsor:**
  - No clinically relevant DDI with Glyburide (AUC and Cmax values of naltrexone of 1.9- and 2.1- fold, respectively, and bupropion 1.4- and 1.2- fold, respectively – claimed to be effect of glucose solution)
  - No clinically relevant DDI with Valsartan, Atorvastatin, Nifedipine (58% and 24% increase in **B** Cmax and AUC), and Lisinopril
  - 2 and 4-fold increase in metoprolol Cmax and AUC, respectively
- **Review Questions:**
  - What is the effect of NB on other co-administered drugs and vice-versa?
  - Does the DDI result warrant for any dose adjustments for NB and the co-administered drugs?
  - Are analytical methods adequate?
- **Filing Comments:**
  - None

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Specific Populations – Ger, RI, HI

- **Sponsor:**
  - Ger, RI, HI not evaluated for NB, referenced to approved labels and literature information
  - Pooled analysis from Phase 1 studies to evaluate Race and Gender Effects did not reveal any remarkable differences in PK
  - No dose adjustments based on BMI, in elderly (renal function monitoring) (b) (4)
  - To be used with caution in patients with (b) (4)
  - Not be used in nursing mothers, (b) (4)
- **Review Questions:**
  - Are sponsor's assessments appropriate and do they adequately support the proposed labeling language?
- **Filing Comments:**
  - None

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Comparability of TBM Formulation

- **Sponsor:**
  - NB TBM Formulation claimed equivalent to **N** IR and to Wellbutrin SR dose normalized AUC (**NB-230**)
  - Comparable PK of marketed naltrexone IR (50 mg) tablet, a marketed bupropion SR (150 mg) tablet, and the intended NB commercial drug product (**NB-230**)
  - Approx dose-proportionality 4/90 and 8/90 tablets (**NB-232**)
  - Phase 3 ((b) (4) and TBM (b) (4) formulations compared to and claimed to be bioequivalent w. r. to NB-Cmax and AUC except naltrexone Cmax, which was 15% lower for the TBM har (b) (4) (**NB-228, 229**)
- **Review Questions:**
  - What is the relative bioavailability of TBM in comparison to the formulations used in the development phase?
  - Are analytical me hods adequate?
- **Filing Comments:**
  - None

GRMP Filing Checklist:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 200063 **Applicant: Orexigen Therapeutics** **Stamp Date: 02/23/2010**

Drug Name: **Naltrexone/Bupropion**

NDA/BLA Type: Combination drug product (505(b)(2))

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	**X**		To be marketed formulation has been used in the pivotal clinical trials. BE trials compared Phase 2 and Phase 3 formulations.
2	Has the applicant provided metabolism and drug-drug interaction information?	**X**		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	**X**		Sponsor have not submitted control files for the population PK analysis and a request will be communicated in the filing letter
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			**NA**
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	**X**		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	**X**		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	**X**		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	**X**		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			**NA** Sponsor has requested a full waiver from conducting pediatric studies for patients from (b) (4) years of age.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			**NA**

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

MANOJ KHURANA	07/19/10
Reviewing Pharmacologist	Date
SALLY CHOE	07/19/10
Team Leader/Supervisor	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

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

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

/s/

MANOJ KHURANA
08/03/2010

SALLY Y CHOE
08/03/2010