A Double-Blind, Placebo-, Bupropion- and Naltrexone-Controlled Study of the Efficacy and Safety of Three Doses of Naltrexone-Bupropion SR Combination Therapy in Obesity: Effects on Total and Visceral Adipose Tissue and CV Risk Markers

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ABSTRACT

Introduction: The NB-201 study (n=419 randomized) compared the efficacy and safety of bupropion SR 200 mg BID combined with naltrexone IR 16, 32 or 48 mg/day (NB16, NB32, NB48) against bupropion SR 200 mg BID, naltrexone 48 mg/day, or placebo for 24 weeks followed by a 24 week extension period. A subset of subjects also underwent DEXA and multi-slice abdominal CT scans to assess effects of therapy on abdominal and overall adipose tissue.

Results: Subjects randomized to NB combination therapy groups achieved 1.5- to 2-fold greater weight loss after 24 weeks of treatment than subjects randomized to placebo or monotherapy, with weight loss among the NB groups greater than the additive effects observed for the two individual monotherapy groups. Additional weight loss with NB was also evident through 48 weeks.

A subset of 75 randomized subjects had a DEXA scan and 73 randomized subjects had an abdominal CT scan at baseline and at 24 weeks. No relevant baseline differences were detected among all randomized subjects. LSmean change from baseline in total body adiposity was -14.0% for the combined NB groups, compared to -4.0%, -3.2% and -4.1% for the placebo, naltrexone- and bupropion-monotherapy groups, respectively (all 3 p-values ≤ 0.01). LSmean change from baseline in visceral adiposity for the combined NB groups was -15.0%, compared to -4.6%, -0.1% and -2.3% for the placebo, naltrexone- and bupropion-monotherapy groups, respectively (all 3 p-values ≤ 0.01). Beneficial effects associated with NB therapy were also observed in serum insulin, triglycerides, HDL cholesterol, plasma glucose, and waist circumference.

Conclusions: The beneficial effects of NB therapy on total body weight include synergistic reduction of adipose tissue. DEXA scans indicated that the total body fat loss and the body weight loss of the combination were greater than the sum of the two component drugs demonstrating synergy of the combination. Visceral adipose tissue is associated with insulin resistance and increased cardiovascular risk. Loss of visceral adipose tissue with NB therapy was also significantly greater than the sum of the monotherapies.

INTRODUCTION

Contrave™ is a combination of naltrexone (N) with bupropion (B) in phase III clinical development for obesity treatment. This approach is designed to promote hypothalamic proopiomelaocortin (POMC) activity (appetite reduction and increase in energy expenditure) while minimizing auto-inhibition by endogeneous beta-endorphin. This mechanism of action is expected to prevent early weight loss plateau.

OBJECTIVES

To assess the efficacy of the combination of naltrexone with bupropion on weight loss and test the hypothesis that the combination of naltrexone with bupropion improves markers of CV risk and insulin resistance. We also sought to explore whether the addition of N to B would improve long-term weight loss and shift the expected plateau observed with other weight loss therapies.

METHODS

A double-blind, 24-week, placebo-controlled multi-center trial with a 24-week extension for the NB and bupropion monotherapy groups, which randomized 419 healthy, non-diabetic, obese subjects to either: bupropion 200 mg bid, placebo, naltrexone 48 mg daily dosed bid, or bupropion with naltrexone 16, 32 or 48 mg daily dosed bid. At baseline, 12 and 24 weeks, subjects were provided an exercise prescription and a 500 kcal/day deficit diet. A subset of 75 subjects had a DEXA scan to measure body fat (Hologic QDR 4500) and 73 subjects had multislice abdominal CT scan data to measure visceral fat (8 x 10mm slices every 5 cm from the pelvis to the dome of the diaphragm followed by integration to kg) at baseline and at 24 weeks.

STATISTICAL METHODS

Analysis: Change from baseline to endpoint was analyzed using an ANOVA model with treatment as a fixed effect. Categorical response was analyzed using Chi-square. Analysis on the intent-to-treat (ITT) population used the LOCF approach, whereas analysis on the completer population was based upon Week 24 and Week 48 observed data. DEXA, abdominal CT, insulin, glucose and lipid analyses were performed on the Week 24 completer population.

Derivations: QUICKI = 1 / [log(Insulin µU/ml) + log(Glucose mg/dL)]. HOMA = [Glucose mmol/l x Insulin µU/ml] / 22.5. Log(HOMA) = log(base 10) of HOMA.

RESULTS (Figures 1, 2 and 3)

Weight Loss: NB-treated subjects demonstrated statistically significantly greater total body weight loss (a 1.5- to 2-fold difference) compared with placebo – or monotherapy-treated subjects. In the ITT analysis, the greatest weight loss effects were observed for the NB32 and NB16 dose groups. NB- treated subjects also demonstrated greater improvement compared with placebo- and monotherapy-treated subjects in response rates and completer analysis. Figure 3 shows continuing weight loss through 48 weeks for the three combination therapies where as bupropion demonstrates a weight loss plateau.

Figure 1: LSMean Percent Change from Baseline in Body Weight (Week 24)

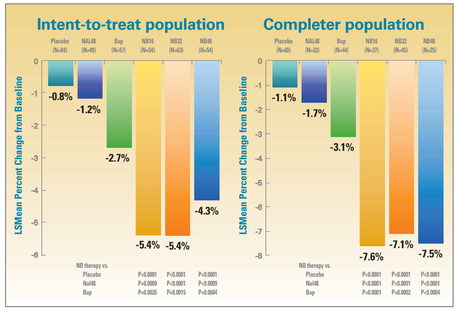


Figure 2: Categorical Response At Least 5% Change from Baseline in Body Weight (Week 24)

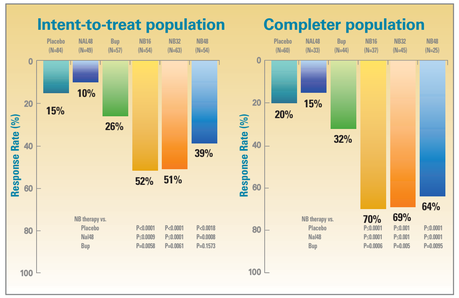
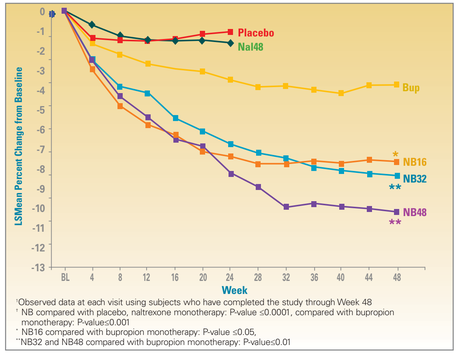


Figure 3: LSMean Visitwise Percent Change from Baseline (Week 48) Completer Population[1]



[1]Observed data at each visit using subjects who have completed the study through Week 48
* NB compared with placebo, naltrexone monotherapy: P-value ≤0.0001, compared with bupropion monotherapy: P-value≤0.001
^ NB16 compared with bupropion monotherapy: P-value ≤0.05,
**NB32 and NB48 compared with bupropion monotherapy: P-value≤0.01

Safety and Tolerability: There were no serious adverse events related to NB therapy. Nausea was the most common treatment-emergent adverse event (TEAE), associated with increasing naltrexone dose. Nausea typically occurred in the first few weeks of exposure, was transient and mild or moderate in severity. Other common TEAEs included headache, dizziness and insomnia. There was no indication of meaningful adverse effects of NB therapy on vital signs, ECG intervals, laboratoy evaluations or depression measures. No treatment-associated worsening of mood/suicidality relative to placebo was observed.

Total and Visceral Fat Weight Loss: DEXA scans indicated that the percent of weight loss from total body fat was numerically greater than the total body weight loss. Visceral adipose tissue loss with NB therapy was significantly greater compared with placebo or the monotherapies, a marker of potential associations between decreased cardiovasuclar risk and NB therapy. (Table 1).

Table 1: LSMean Percent Change from Baseline (±SE) Week 24 Completer Population

	Placebo	Nal48	Bup	NB-Pooled
DEXA Fat Mass (% change)	-4.0 + 2.0 ***	-3.2 + 2.5 ***	-4.1 + 2.9 **	-14.0 + 1.3
CT Measured Visceral Fat (% change)	-4.6 + 2.7 **	-0.1 + 3.5 ***	-2.3 + 4.2**	-15.0 + 1.8

Comparisons with NB-Pooled (all 3 NB doses): *P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.
[1]24 Week Subset Completer Population

Serum Lipids and Markers of Insulin Resistance: The most marked treatment effects were observed in the NB32 therapy group which had the best combination therapy subject retention rates. NB32-treated subjects demonstrated statistically significantly greater improvement compared with placebo- and monotherapy- treated subjects in fasting glucose, log(homa) and QUICKI. Significant improvements were also observed compared with at least one of the control groups in waist circumference, insulin, triglycerides, and HOMA (Table 2).

Table 2: LSMean Change from Baseline (±SE) Week 24 Completer Population

	Placebo	Nal48	Bup	NB32
Weight (% change)[1]	-1.1 ± 0.6***	-1.7 ± 0.9**	-3.1 ± 0.7***	-7.1 ± 0.7
DEXA Fat Mass (% change)[2]	-4.0 ± 2.0**	-3.2 ± 2.5**	-4.1 ± 2.9**	-12.0 ± 1.7
CT Measured Visceral Fat (% change)[2]	-4.6 ± 2.7**	-0.1 ± 3.6**	-2.3 ± 4.3*	-14.0 ± 2.4
Waist (cm)[1]	-1.0 ± 5.4**	-3.8 ± 12.7	-2.9 ± 6.0	-5.4 ± 7.6
Fasting Glucose (mg/dL)[1]	1.9 ± 1.3*	3.4 ± 1.7*	3.5 ± 1.5*	-2.0 ± 1.5
Insulin (µU/mL)[1]	0.9 ± 0.9**	1.7 ± 1.3**	-0.5 ± 1.1	-3.0 ± 1.1
Triglyceride (mg/dL)[1]	-15.0 ± 7.7*	-17.6 ± 10.4	-18.4 ± 9.0*	-43.6 ± 8.8
HOMA[1]	0.3 ± 0.2**	0.5 ± 0.3**	-0.1 ± 0.3	-0.8 ± 0.3
Log (HOMA)[1]	0.023 ± 0.029**	0.037 ± 0.039**	-0.004 ± 0.034*	-0.141 ± 0.033
QUICKI[1]	-0.002 ± 0.003***	-0.003 ± 0.004**	-0.000 ± 0.004**	0.017 ± 0.004

Comparisons with NB32: *P-value ≤ 0.05; **P-value ≤ 0.01; ***P-value ≤ 0.001.
[1]24 Week Completer Population from overall NB-201 study
[2]24 Week Subset Completer Population

SUMMARY and CONCLUSIONS

Combination therapy with naltrexone and bupropion (NB) is associated with acceptable safety and tolerability and significantly greater weight loss than with placebo or the monotherapies. These results further validate and extend the preclinical and previously reported clinical results (Study OT-101) and demonstrate a bupropion-naltrexone synergy on weight loss. Additionally, NB appears to improve markers of cardiovascular risk and insulin resistance. Naltrexone-bupropion weight loss synergy is a novel observation and invites additional research to better understand the Contrave™ mechanisms of action and resulting potential for weight loss and metabolic/glycemic control in obesity.

REFERENCES

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