Overview of Naltrexone / Bupropion Phase 3 Clinical Development Program

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Disclosures

- Consulting: Orexigen, Takeda, iNova, Vivus, Novo Nordisk, Biologix, Amgen, Eisai, Novartis, Rhythm
- Boards of Directors: The Obesity Society, Obesity Action Coalition, Obesity Treatment Foundation, True Health Initiative, NASH Alliance, Global Liver Institute
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Naltrexone/Bupropion Phase 3 Trials

	NB-301 (COR-I)[1] N=1742	NB-303 (COR-II)[2] N=1496	Intensive Counseling NB-302 (COR-BMOD)[3] N=793	Type 2 diabetes NB-304 (COR-DM)[4] N=505
Study Design	56 weeks, placebo-controlled, including 3-week dose escalation (COR-II: primary endpoint 28 weeks)			
Population	BMI 30–45 kg/m² BMI 27–45 kg/m² (with comorbidities)			T2DM, BMI 27–45 kg/m²
Diet and Exercise	Diet and exercise counseling		Intensive BMOD[a]	Diet and exercise counseling
Dose and Randomisation	NB16 and NB32 1:1:1	NB32 2:1	NB32 3:1	NB32 2:1

[a]BMOD consisted of group sessions led by dietitians, psychologists, or exercise specialists to educate subjects on weight control techniques. Subjects were also asked to follow individualized hypocaloric diets and were encouraged to increase moderately vigorous physical activity from 180 min/week to 360 min/week. BMI=body mass index; BMOD=behavior modification; NB16=naltrexone 16 mg SR/bupropion 360 mg SR; NB32=naltrexone 32 mg SR/bupropion 360 mg SR; T2DM=type 2 diabetes mellitus. **1.** Greenway FL et al. *Lancet*. 2010;376:595-605. **2.** Apovian CM et al. *Obesity*. 2013;21:935-943. **3.** Wadden TA et al. *Obesity*. 2011;19:110-120. **4.** Hollander P et al. *Diabetes Care*. 2013;36:4022-4029.

Key Inclusion and Exclusion Criteria

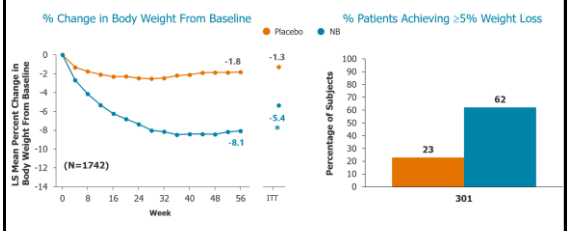
- Inclusion:
  - BMI 30-45 kg/m² (or 27-45 m² with controlled comorbidities)
  - Male / female, 18 – 65 yrs old
- Exclusion
  - Pregnancy/lactation
  - Type 1 diabetes
  - Cerebrovascular, cardiovascular, hepatic or renal disease
  - History of bariatric surgery
  - History of seizures or psychiatric illness
  - History of naltrexone or bupropion treatment within 12 months
  - Uncontrolled hypertension
  - No additional weight loss drugs allowed

1. Greenway FL et al. *Lancet*. 2010;376:595-605. **2.** Apovian CM et al. *Obesity*. 2013;21:935-943. **3.** Wadden TA et al. *Obesity*. 2011;19:110-120. **4.** Hollander P et al. *Diabetes Care*. 2013;36:4022-4029.

Baseline Characteristics

Age	▪ Mean=**46 years**
Sex	▪ Men: **17%** ▪ Women: **83%**
BMI	▪ Mean=**36 kg/m²**
Waist Circumference	▪ Mean=**110 cm**
Race	▪ White: **77%** ▪ Black: **18%** ▪ Other: **5%**
Comorbidities	▪ Hypertension: **24%** ▪ Dyslipidaemia: **54%** ▪ Type 2 diabetes: **10%**

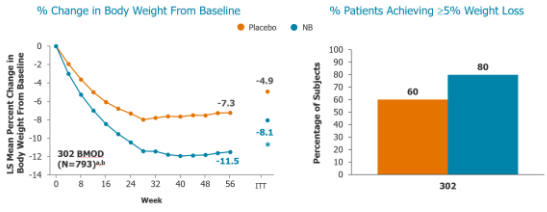
Weight Loss in COR-I



Observed least squares mean (SE) percentage change from baseline in body weight and number of participants at each visit during 56 weeks.
*p<0.0001 compared with placebo.

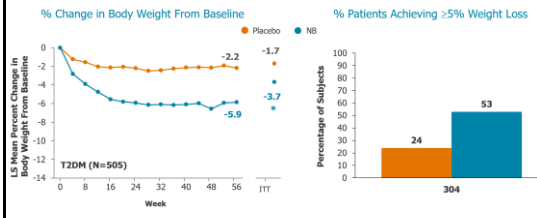
1. Greenway FL et al. Lancet. 2010;376:595-605.

Weight Loss in COR-BMOD



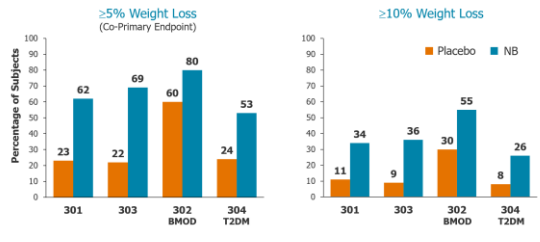
1. Wadden TA et al. *Obesity*. 2011;19:110-120.

Weight Loss in COR-DM



1. Hollander P et al. *Diabetes Care*. 2013;36:4022-4029

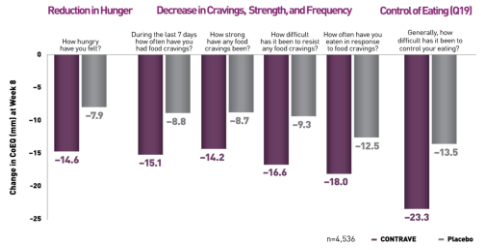
Categorical Weight Loss Across Trials



*P<0.01 vs placebo; **P<0.001 vs placebo.
BMOD=behavior modification; DM=diabetes mellitus; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares.

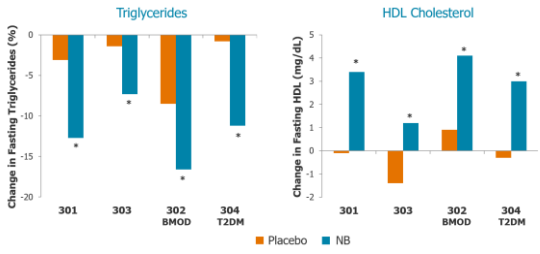
Greenway FL et al. *Lancet*. 2010;376:595-605. Wadden TA et al. *Obesity*. 2011;19:110-120. Hollander P et al. *Diabetes Care*. 2013;36:4022-4029.

Control of Eating Improves as Early as Week 8

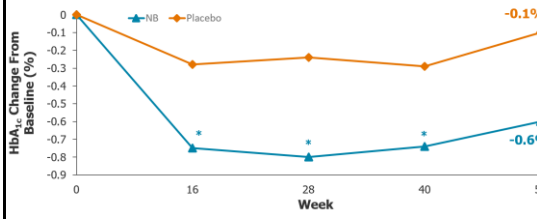


Dalton M, Finlayson G, Hill A, Blundell J. Preliminary validation and principal components analysis of the Control of Eating Questionnaire (CoEQ) for the experience of food craving. *Eur J Clin Nutr*. 2015;69:1313-1317.

Changes in Lipids Across Trials



Changes in HbA1c in Patients with T2D



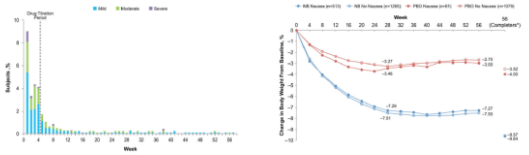
1. Hollander P et al. *Diabetes Care*. 2013;36:4022-4029

Adverse Effects Across Clinical Trials

Adverse Reaction	Naltrexone/Bupropion n=2545	Placebo n=1515
Nausea	32.5%	6.7%
Constipation	19.2%	7.2%
Headache	17.6%	10.4%
Vomiting	10.7%	2.9%
Dizziness	9.9%	3.4%
Insomnia	9.2%	5.9%
Dry mouth	8.1%	2.3%
Diarrhea	7.1%	5.2%

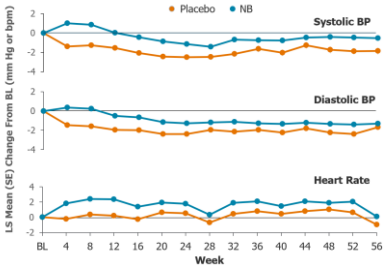
*Adverse events occurring in greater than 2% of patients are shown.
Contrave [prescribing information]. La Jolla, CA: Orexigen Therapeutics, Inc.; 2016.

Weight Loss is Independent of Nausea



Hong, K. et al 2014. Clinical obesity 6, 305-312

Changes in Blood Pressure and Heart Rate

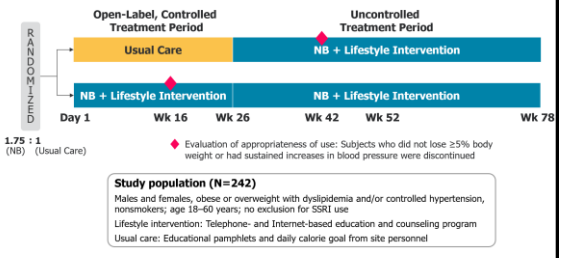


Primary safety dataset, repeated measures analysis.
1. US FDA Contrave (naltrexone SR / bupropion SR combination) Advisory Committee Briefing Document; NDA 200063; 2010.

Summary of Clinical Trial Data

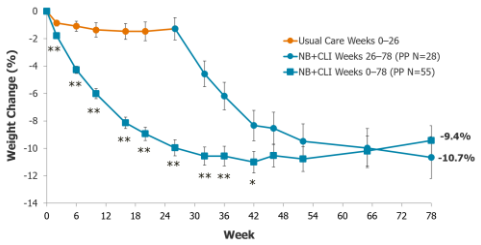
- Naltrexone/bupropion for weight loss has been assessed for safety and efficacy across 4 phase 3 trials and 4536 patients
- Naltrexone/bupropion treatment for 56 weeks results in significantly greater weight loss than placebo
- Nausea is the most common side effect of treatment, but is rarely severe and occurs primarily during dose escalation phase

Naltrexone/Bupropion in Real-World Use



Halseth AE, et al. *Obesity.* 2016; doi:10.1002/oby.21726. Halseth AE, et al. Presented during Obesity Week; November 4-6, 2015; Los Angeles, CA.

Naltrexone/Bupropion in Real-World Use



*P<0.05; **P<0.001; †Data are LS mean (SE) from study completers.
CLI=comprehensive lifestyle intervention
Halseth AE, et al. Obesity. 2016; doi:10.1002/oby.21726.