



OREXIGEN[®]

Addressing the
Growing Gap in Obesity Treatment

Poised for Regulatory and Commercial Success



Forward-Looking Statements



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Contrave Obesity Research (COR)
Phase III Program Summary

July 2009

Efficacy

Additional
Endpoints

Experience in
Diabetes

Safety /
Tolerability

Statistical Significance on Co-Primary Weight Loss Endpoints

Efficacy Benchmark

- Categorical response: $\geq 35\%$ of patients on drug lose at least 5% of their body weight and that the proportion is double placebo
 - OR -
- Mean weight loss: $\geq 5\%$ difference between active product and placebo group

Additional Endpoints:

- Study markers of CV and metabolic risk

Experience in Diabetes

- Study measures of glycemic control

Trial Size & Duration

- $\geq 3,000$ subjects randomized to active doses of the product and $\geq 1,500$ subjects randomized to placebo for 1 year of treatment

Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

Key elements of FDA guidance:

	Total Program (n=4,536)
Statistical Significance on Co-Primary Weight Loss Endpoints	✓
Efficacy Benchmark (5% Categorical Response OR 5% Placebo Subtracted AND $p \leq 0.05$)	✓
Additional Endpoints	✓
Efficacy in Obese Patients with Diabetes	✓
Sufficient Patient Exposures for Evaluation of Safety and Tolerability (1 year)	✓

Phase III Program Designed for Regulatory and Commercial Success



Contrave Obesity Research	Trial	Patients Enrolled	Key Features
COR – I	NB-301	1,742	Two Doses (Contrave16 and Contrave32)
COR – II	NB-303	1,496	Contrave32 with Re-randomization (Contrave32 or 48) for Non-responders after Week 28
COR-Diabetes	NB-304	505	Contrave32 in Type 2 Diabetes
COR-BMOD	NB-302	793	Contrave32 with Intensive Behavioral Modification

Common Features

- Double blind, placebo controlled 56 week trials with initial titration
- Primary endpoints: proportion achieving $\geq 5\%$ weight loss and % change body weight
- ITT-LOCF: all randomized patients with ≥ 1 post-baseline observation while on study drug
- Obese patients with BMI 30-45 (kg/m^2), or 27-45 (kg/m^2) with co-morbidities
- Additional endpoints include markers of cardiometabolic risk, eating control, depression and quality of life

Baseline Characteristics



Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

	NB-301	NB-303	NB-304
Average Age	44	44	54
Sex, Female	85%	85%	56%
Race, White	75%	84%	79%
Tobacco Use	34%	37%	46%
Weight (kg)	100	100	106
BMI	36	36	37
Waist Circumference (cm)	109	109	115
Systolic BP (mm Hg)	119	118	125
Diastolic BP (mm Hg)	77	77	77
Pulse	72	71	73
Baseline Hypertension	22%	22%	62%
Baseline Dyslipidemia	51%	55%	84%

Note: Represents baseline characteristics for both Contrave and placebo patients in each trial

Met Co-primary Endpoints and Exceeded FDA Benchmark in Large Phase III Trials



Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

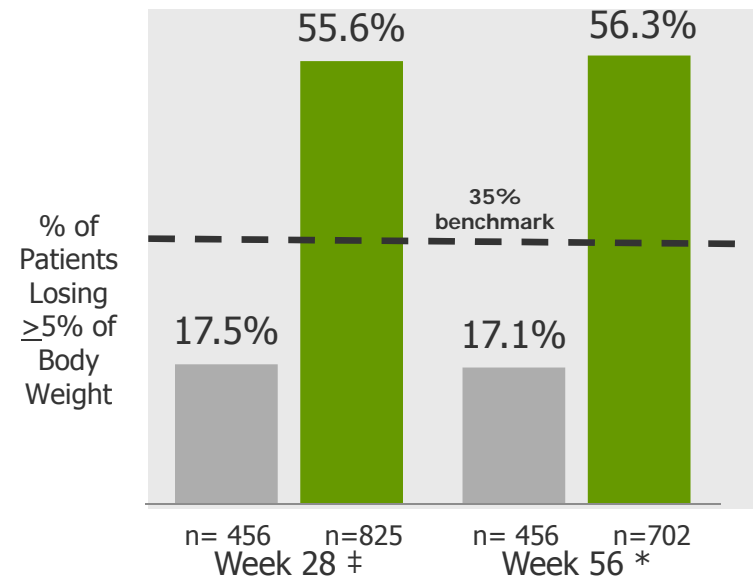
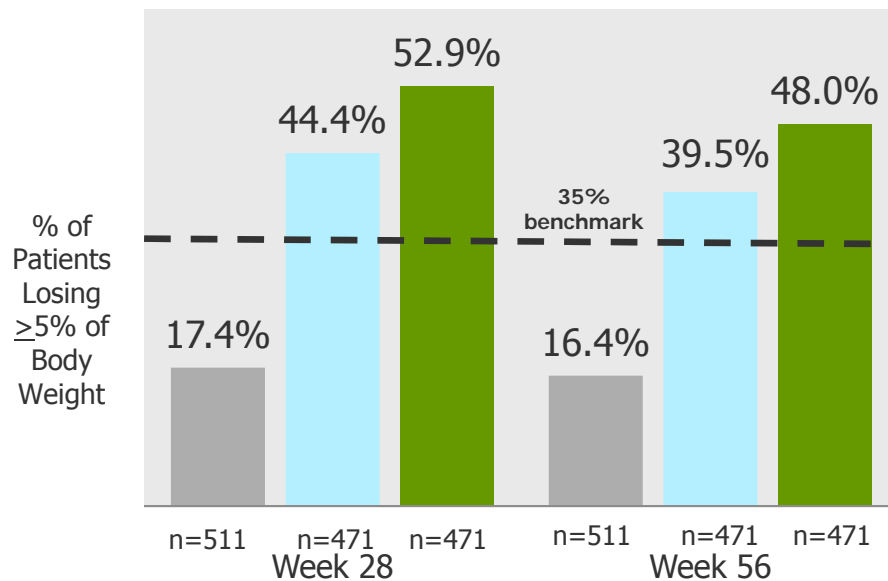
NB-301 Results

5% Categorical Analysis (ITT-LOCF)

NB-303 Results[^]

5% Categorical Analysis (ITT-LOCF)

Placebo Contrave16 Contrave32



Note: All differences between Contrave and placebo highly statistically significant at $p \leq 0.001$

[^] Results of re-randomized Contrave48 group not shown; no statistical difference from re-randomized Contrave32 group

‡ Primary Endpoint

* Weighted LOCF

Contrave Mean Weight Loss Supports Overall Program Efficacy



Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

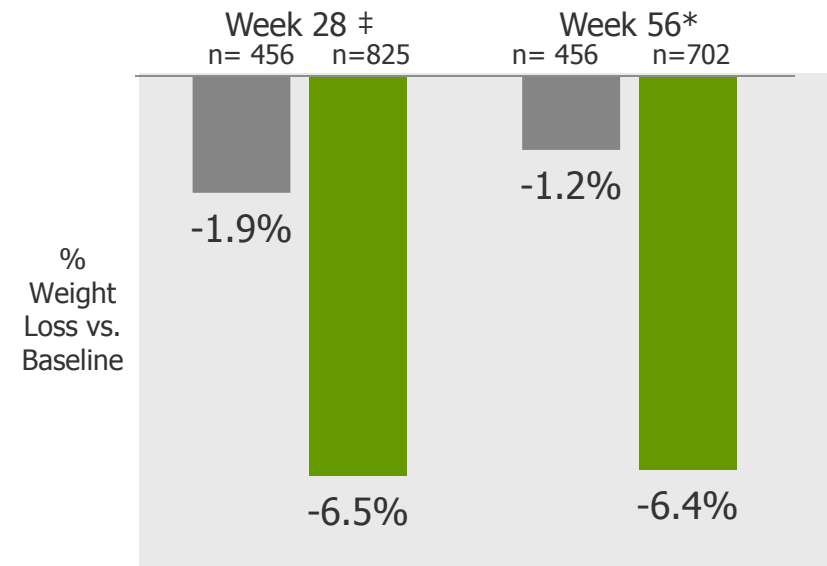
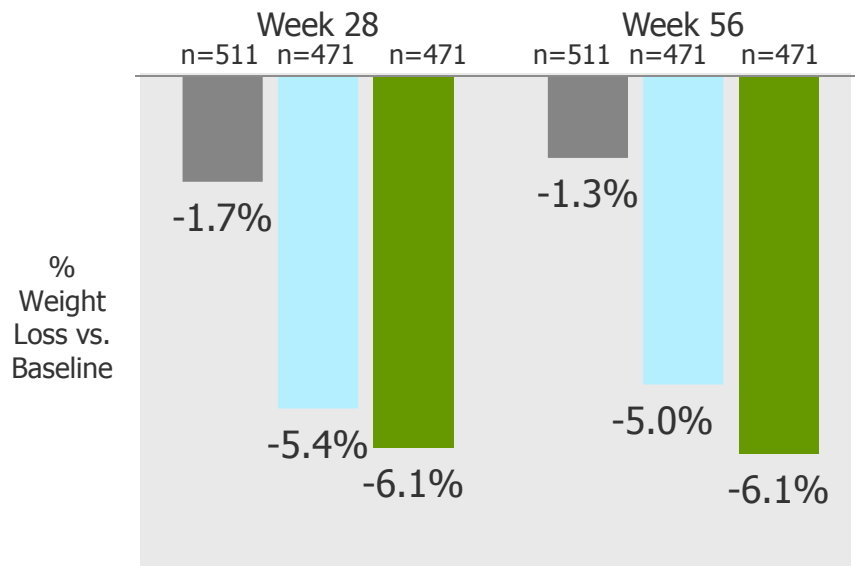
NB-301 Results

Mean % Weight Loss (ITT-LOCF)

NB-303 Results ^

Mean % Weight Loss (ITT-LOCF)

■ Placebo ■ Contrave16 ■ Contrave32



Note: All differences between Contrave and placebo highly statistically significant at $p \leq 0.001$

^ Results of re-randomized Contrave48 group not shown; no statistical difference from re-randomized Contrave32 group

‡ Primary Endpoint

* Weighted LOCF

Contrave Demonstrated Sustained Weight Loss Over a Year of Treatment



Efficacy

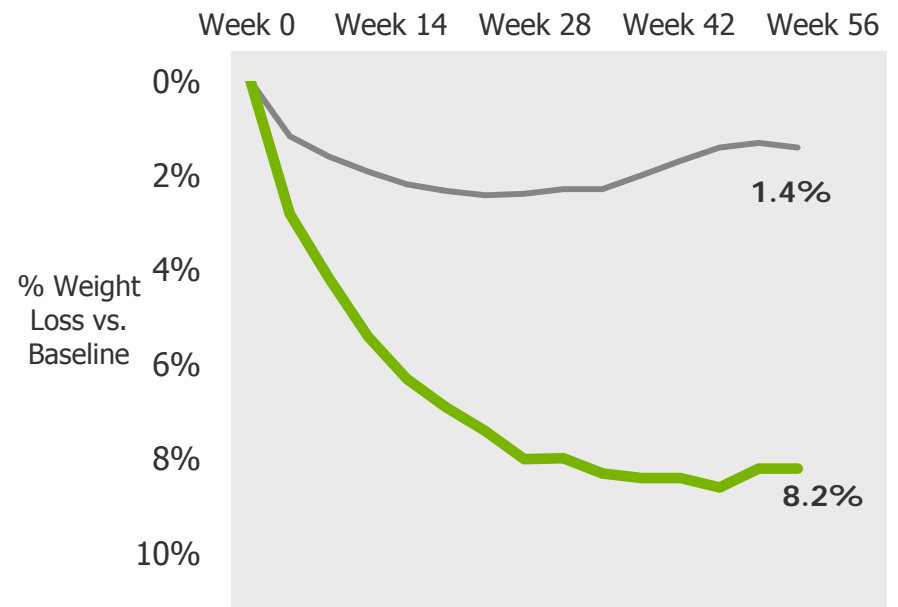
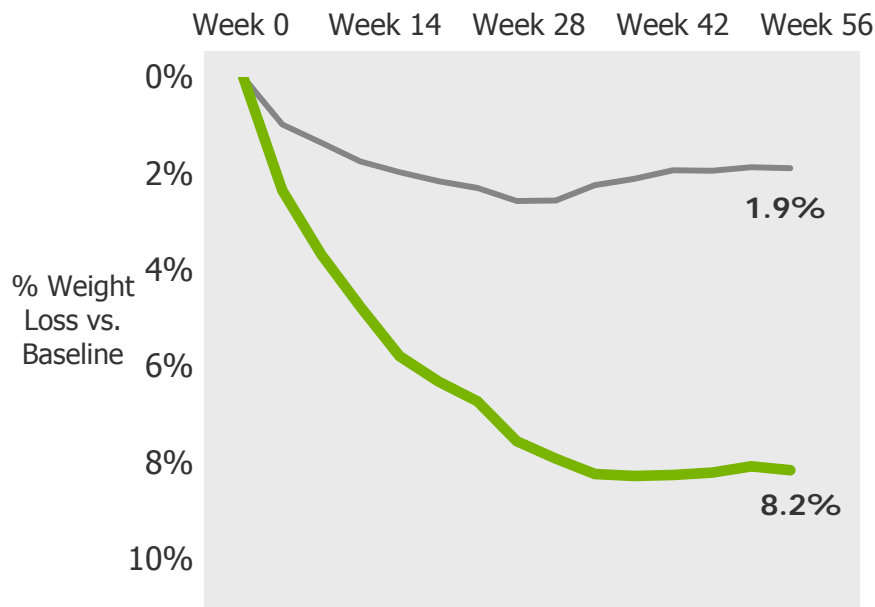
Additional Endpoints

Experience in Diabetes

Safety / Tolerability

NB-301 Observed Case Weight Loss

NB-303 Observed Case Weight Loss *



* Contrave32 weighted analysis



Contrave Demonstrated Improvement in Markers of Cardiometabolic Risk



Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

Key Secondary Efficacy Endpoints (ITT-LOCF)	NB-301 / NB-303
10% Categorical Response	Improved ¹
Waist Circumference	Improved ¹
Fasting HDL Cholesterol	Improved ¹
Fasting Triglycerides	Improved ¹
Fasting Insulin	Improved ²
Fasting Blood Glucose	Improved ²
Fasting LDL Cholesterol	Improved ²
Body Composition Sub-study	
Total Body Fat (CT)	Improved ¹
Total Visceral Fat (DEXA)	Improved ¹

¹ Significant difference between Contrave and placebo ($p \leq 0.05$) in NB-301 or NB-303

² Unadjusted p-value ≤ 0.05 in NB-301 or NB-303

Contrave Treatment Demonstrated Improvement in Patient-reported Outcomes



Patient-reported Outcomes (ITT-LOCF)	NB-301 / NB-303
Quality of Life (IWQOL-Lite)	Improved ¹
Control of Eating Questionnaire	
Hunger	Improved ²
Fullness	Improved ²
Cravings	Improved ²
General control of eating	Improved ²
Symptoms of Depression (IDS-SR total score)	Similar to placebo ³

¹ Significant difference between Contrave and placebo ($p \leq 0.05$) in NB-301 or NB-303

² Unadjusted p-value ≤ 0.05 in NB-301 or NB-303

³ Change from baseline to endpoint, ITT-LOCF

Contrave Exceeded FDA Benchmark in Obese Patients with Diabetes



Efficacy

Additional Endpoints

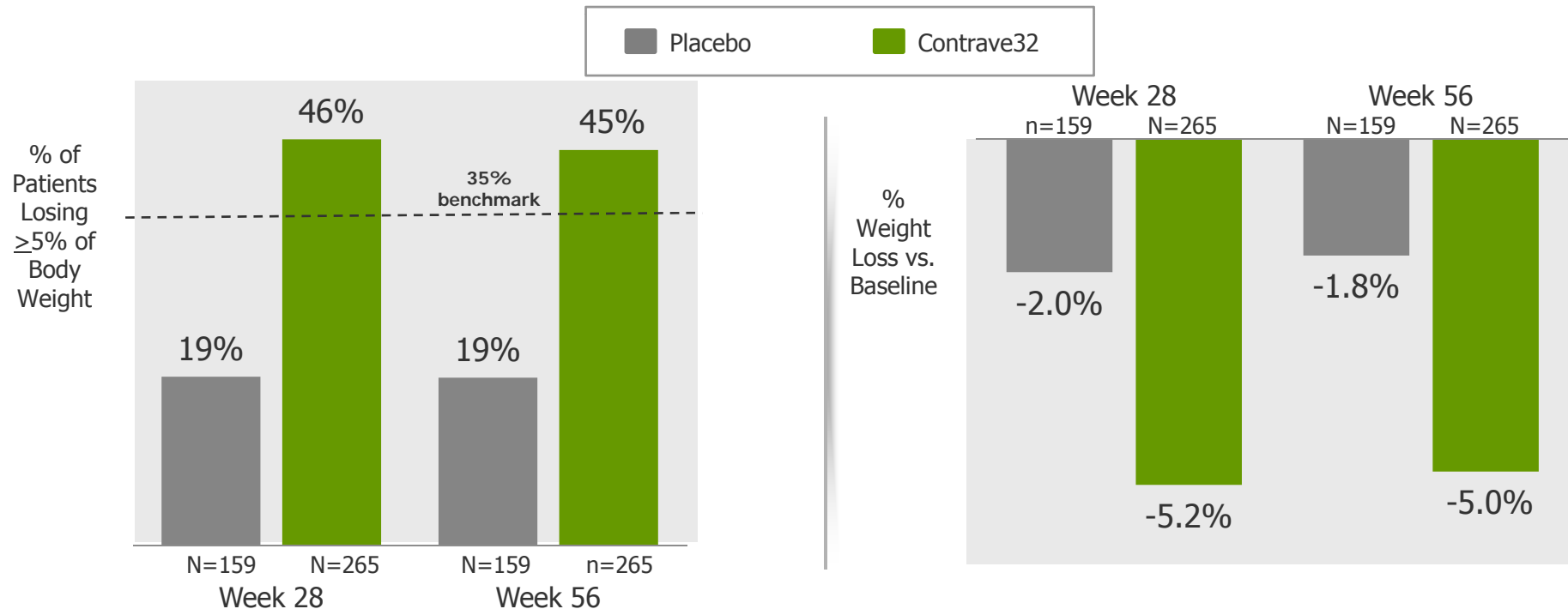
Experience in Diabetes

Safety / Tolerability

NB-304 Results: Contrave32

5% Categorical Analysis (ITT-LOCF)

Mean % Weight Loss (ITT-LOCF)



Note: All differences between Contrave and placebo highly statistically significant at $p \leq 0.001$

Contrave Demonstrated Improved Glycemic Control in Obese Patients with Diabetes



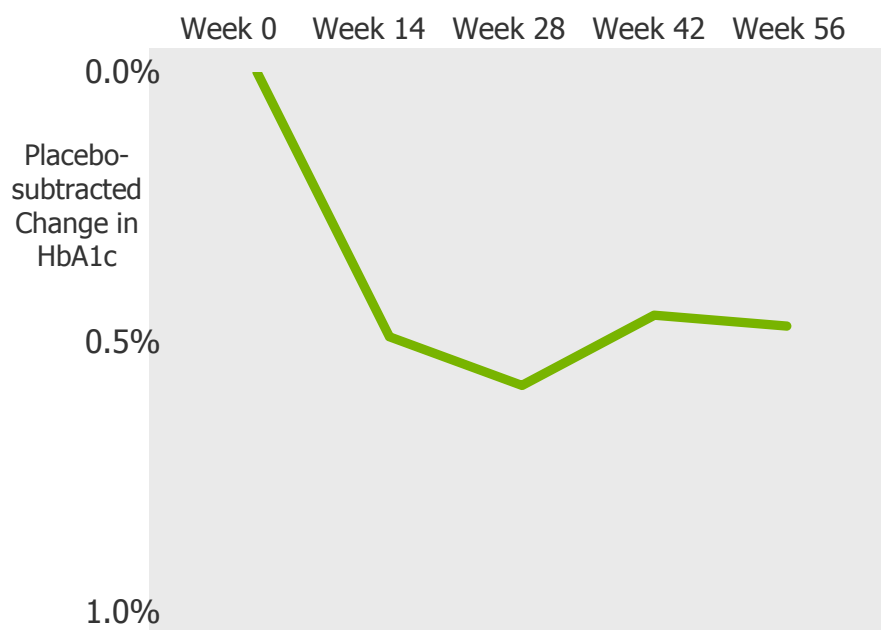
Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

NB-304 Placebo-subtracted HbA1c Observed Case Analysis (Contrave32)



Key Measures (ITT-LOCF)

HbA1c (%)	Improved ¹
% of Subjects with HbA1c <7.0%, <6.5%	Improved ²
% of patients requiring rescue Rx	Improved ²
Fasting HDL	Improved ¹
Fasting triglycerides	Improved ¹

¹ Significant difference between Contrave32 and placebo ($p \leq 0.05$)

² Unadjusted p-value ≤ 0.05

Most Common Treatment-Emergent Adverse Events Across 301, 303, 304



Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

	NB-301 & NB-303		NB-304 (Diabetes)	
	Placebo	Contrave 16	Contrave32	
Overall Treatment-Emergent Adverse Events	68-85%	80%	83-86%	90%
Nausea	5% – 7%	27%	29% – 30%	42% [‡]
Constipation	6% – 7%	16%	16% – 19%	18%
Headache	9%	16%	14 % – 18%	14%
Vomiting	2 % – 4%	6%	9% – 10%	18%
Upper respiratory infection	10% – 11%	9%	9% – 10%	8%
Insomnia	5% – 7%	6%	8% – 10%	11%
Dizziness	3% – 5%	8%	7% – 9%	12%
Dry mouth	2% – 3%	7%	8% – 9%	6%
Nasopharyngitis	5% - 14%	6%	5% – 8%	8%
Diarrhea	4% - 10%	5%	5% – 6%	16%

Note: Represents adverse event experience in trials NB-301, NB-303, NB-304.

[‡] Nausea rate for patients not taking Metformin = 27%

Treatment Discontinuations due to Adverse Events



Efficacy

Additional Endpoints

Experience in Diabetes

Safety / Tolerability

	NB-301 & NB-303		NB-304 (Diabetes)
	Placebo	Contrave16	Contrave32
Overall Discontinuation Rate	41% - 50%	51%	46 - 49%
Discontinuation Rate Due to AEs	10% - 15%	22%	20% - 24%
Nausea	+	5%	6%
Headache	+	2%	1% - 3%
Dizziness	+	2%	+
Vomiting	+	+	+
Depression	0% - 2%	+	+
Insomnia	+	+	+
Anxiety	+	+	+
Diabetes mellitus (worsened)	+	+	+

Note: Represents adverse event experience in trials NB-301, NB-303, NB-304. (> 1% in any arm)

+ Incidence \leq 1%

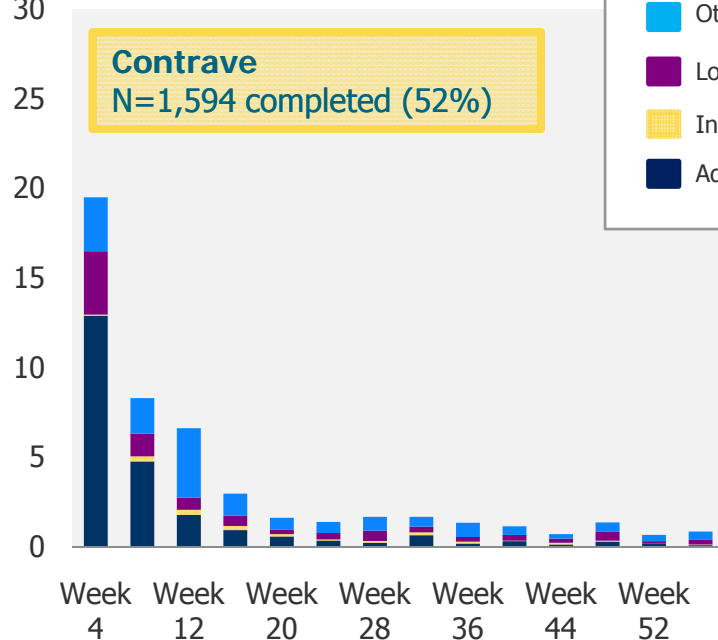
Contrave Phase III Program: Patients who Complete Titration Tend to Remain in Treatment



All Phase III Contrave Treatment Groups

All Phase III Placebo Treatment Groups

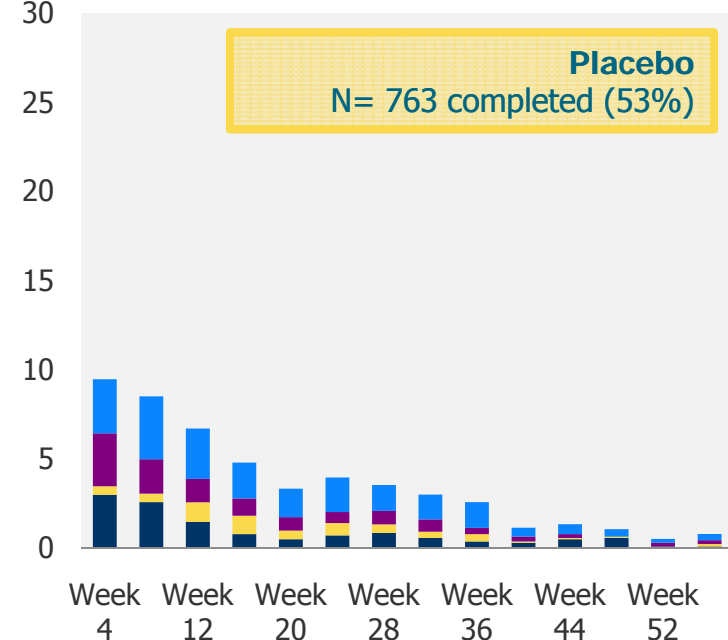
Weekly D/C Rate (%)



Cause of discontinuation

- Other Reason
- Lost to Follow-Up
- Insufficient Weight Loss
- Adverse Event

Weekly D/C Rate (%)

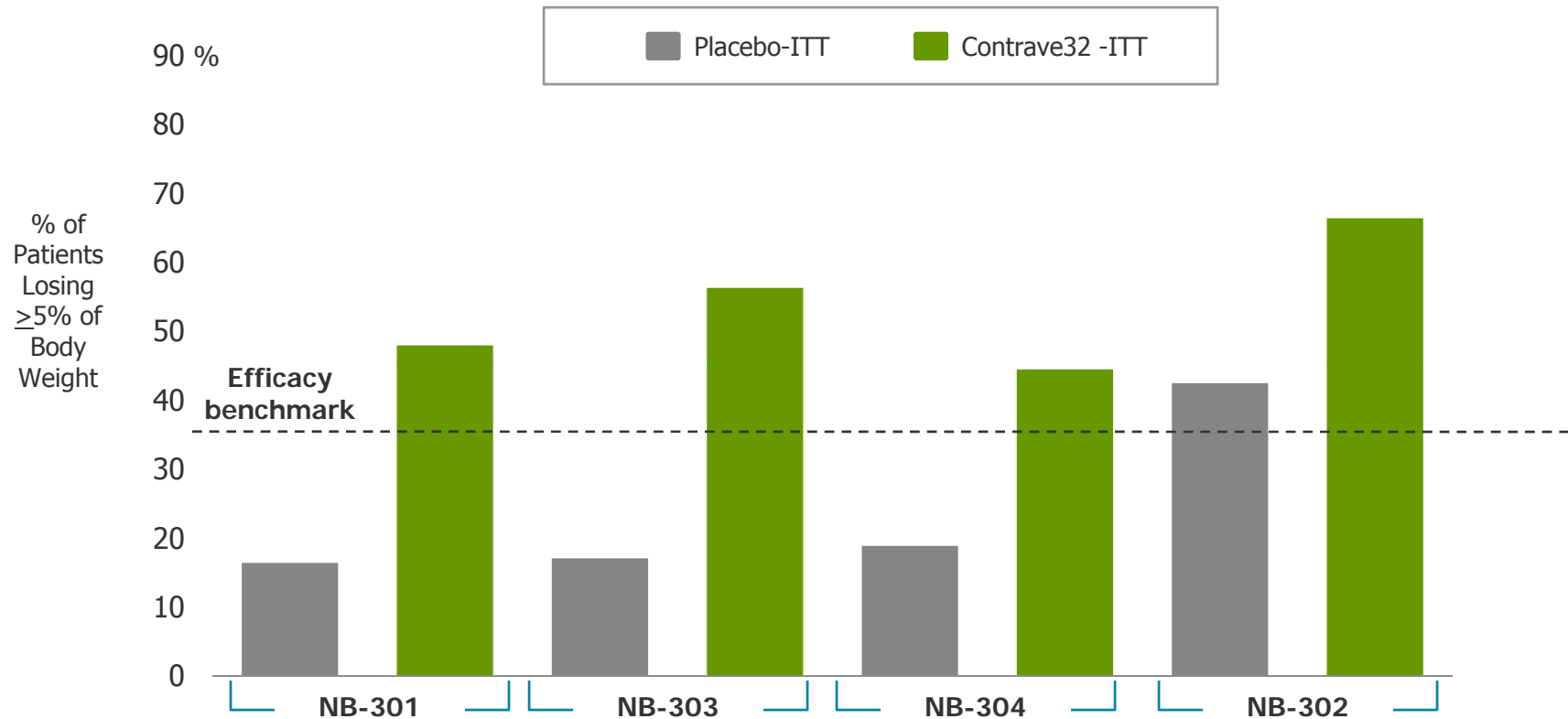


Safety Experience in COR Program



Category	Phase III Program Summary
Serious Adverse Events Attributed to Contrave	Seven events : Cholecystitis (2), seizure (2), palpitations (1), paresthesia (1) and vertigo (1)
Cardiovascular SAEs	Similar rates between Contrave and placebo; one death on Contrave
Depression and Suicidal Ideation	No treatment effects observed. Suicidal ideation: Placebo (3), Contrave (1)
Cardiovascular Effects	
Blood Pressure	<ul style="list-style-type: none"> Contrave patients@ 56 weeks: Mean BP generally unchanged vs. baseline Placebo patients @ 56 weeks: Mean BP slightly decreased (~2mm) vs. baseline Patients losing $\geq 5\%$ weight on Contrave had small decreases in BP at endpoint Contrave treatment did not appear to disrupt the normal circadian BP pattern Elevated blood pressure reported as an AE was higher in the diabetic population (10%) than placebo (4%); D/C for elevated BP on Contrave was uncommon (<1%)
Pulse	There was a slight increase in mean pulse for patients on Contrave (~1 BPM) compared to negligible change on placebo
Labs, ECGs, LFTs	No meaningful treatment effects on ECGs or laboratory measures including liver function tests

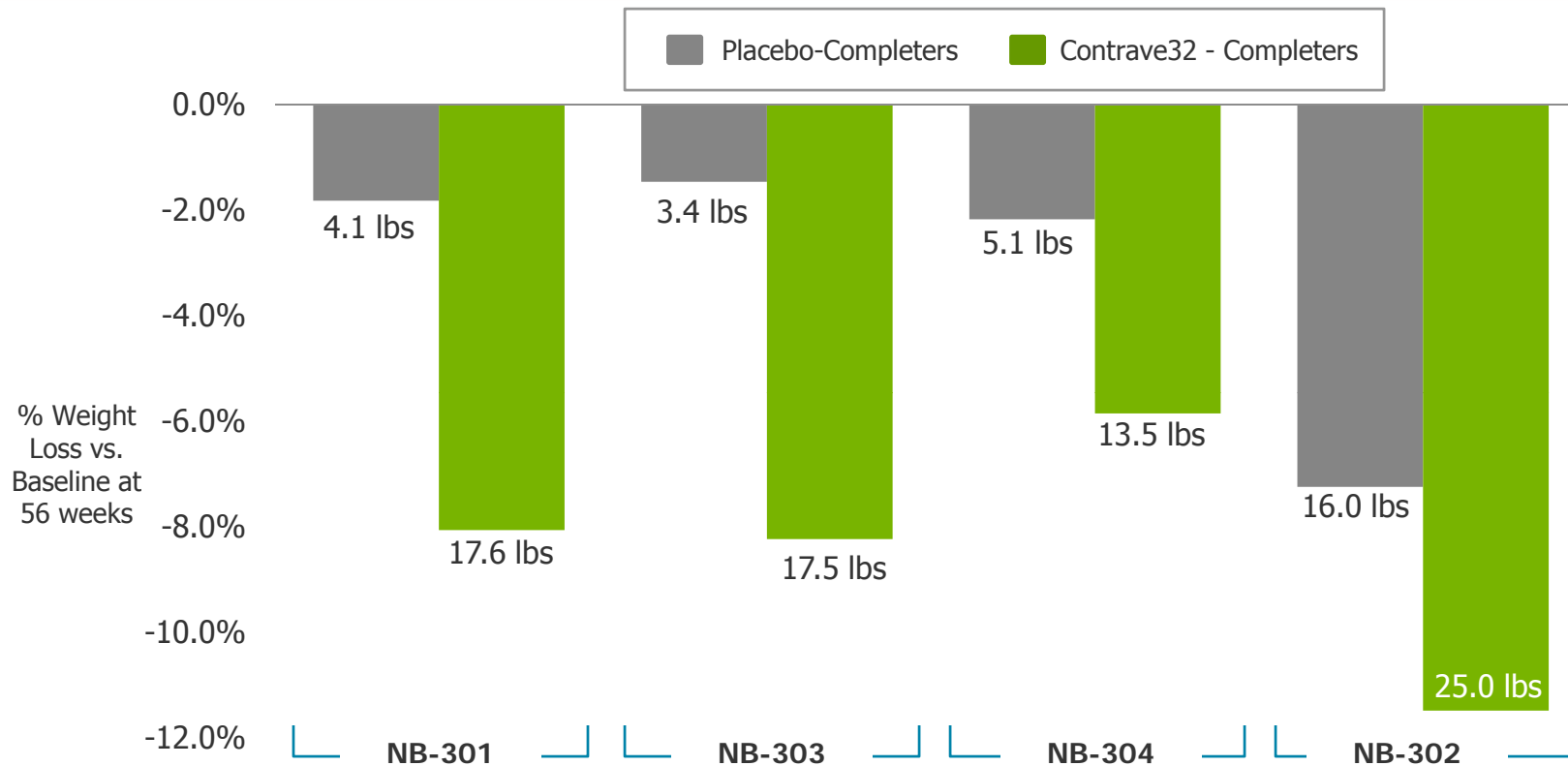
Contrave Exceeded FDA Efficacy Benchmark Across the Phase III Program



Key Conclusions

- In all of our Phase III trials, Contrave crossed the categorical efficacy benchmark
- In NB-301, 303, 304 with typical diet and exercise, Contrave exceeded the 5% categorical benchmark
- In NB-302, with intense behavior modification, Contrave exceeded the 10% categorical benchmark

Patients who Complete One Year of Contrave Therapy Lose Even More Weight



Key Conclusion

Contrave patients in the Phase III program who completed one year of treatment achieved mean weight loss ranging from 5.9% (diabetes) to 11.5% (BMOD). This translates into 14 to 25 lbs, or 20% to 40% of excess weight loss

Orexigen Poised for Transformation on Positive Contrave Results



Commercialization

- NDA Filing in 1H 2010
- Launch Planning Underway
- Partnership for Broader Markets

Differentiation

- Attractive Efficacy and Safety Profile Support Positioning for First-line Therapy
- Contrave Appears to Deliver Unique Benefits to Patients with Uncontrollable Food Cravings

FDA Guidance

- Efficacy
- Additional Endpoints
- Experience in Diabetes
- Safety / Tolerability



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