SUPPLEMENTARY DATA

Supplementary Table 1. Complete list of inclusion and exclusion criteria.

Inclusion Criteria

- Female and male subjects, 18 to 70 years of age
- Have body mass index (BMI) $\geq$ 27 and $\leq$ 45kg/m^2
- Diagnosed with Diabetes Mellitus type 2 and on no injectable hypoglycemic medication or inhaled insulin for more than 3 months
- On oral single or combination hypoglycemic medications (biguanides, thiazolidinediones, meglitinides, α-glucosidase inhibitors, sulfonylureas, DPP4 inhibitors) or no medications for the treatment of type 2 diabetes mellitus. Oral hypoglycemic medication must be stable for at least 3 months prior to randomization
- Systolic blood pressure <145 mm Hg; diastolic blood pressure <95 mm Hg. Anti-hypertensive medications are allowed with the exception of alpha-adrenergic blockers, and clonidine. Antihypertensive treatment must be stable for at least 4 weeks prior to randomization
- Medications for treatment of dyslipidemia are allowed with the exception of cholestyramine and cholestypol as long as medical regimen has been stable for at least 4 weeks prior to randomization
- Free of opioid medication for 7 days prior to randomization
- HbA1c between 7 and 10%, fasting blood glucose <270 mg/ml, fasting triglycerides <400 mg/dL.
- No clinically significant abnormality of serum albumin, blood urea nitrogen, bilirubin, calcium and phosphorus.
- Creatinine levels must be ≤1.4 mg/ dl for women, ≤1.5 mg/dl for men.
- ALT and AST levels within 2.5 x upper limit of normal
- No clinically significant abnormality of hematocrit, white blood cell count, white cell differential, or platelets.
- No clinically significant abnormality on urinalysis
- TSH within normal limits or normal T3, if TSH is below normal limits
- Negative serum pregnancy test in women of child bearing potential
- Negative urine drug screen
- IDS-SR scores <2 on items 5 (sadness), 6 (irritability), 7 (anxiety/tension) and 18 (suicidality), and IDS-SR total score is <30
- If woman of child bearing potential, must be non-lactating and agree to use effective contraception throughout the study period and 30 days after discontinuation of study drug
- Able to comply with all required study procedures and schedule
- Able to speak and read English
- Willing and able to give written informed consent

SUPPLEMENTARY DATA

Exclusion Criteria

- Type 1 Diabetes Mellitus.
- Subjects with “brittle-diabetes” or any hospitalization or emergency room visit due to poor diabetic control within the past 6 months, previous history of diabetes-related dehydration leading to hospitalization, history or evidence of ketoacidosis.
- Obesity of known endocrine origin other than Diabetes Mellitus (e.g., untreated hypothyroidism, Cushing’s syndrome, established Polycystic Ovary Syndrome)
- Diabetes Mellitus secondary to pancreatitis or pancreatectomy.
- Serious medical conditions (including but not limited to ongoing renal or hepatic insufficiency, Class III or IV congestive heart failure; history of myocardial infarction, angina pectoris, claudication, or acute limb ischemia within the previous 6 months; lifetime history of stroke.
- History of malignancy with exception of non-melanoma skin cancer or surgically cured cervical cancer within the previous 5 years
- Loss or gain of more than 5.0 kilograms within previous 3 months
- Severe microvascular or macrovascular complications of diabetes, including but not limited to proliferative retinopathy, active limb ulcerations, amputations of metatarsals or above
- Serious psychiatric illness, including lifetime history of bipolar disorder, schizophrenia or other psychosis, bulimia, and anorexia nervosa; current serious personality disorder, (e.g. borderline or antisocial), current severe major depressive disorder, recent (previous 6 months) suicide attempt or current active suicidal ideation, recent hospitalization due to psychiatric illness.
- A response to Bipolar Disorder questions indicating the presence of Bipolar Disorder
- In need of medications for the treatment of a psychiatric disorder (with the exception of short-term insomnia) within the previous 6 months
- History of drug or alcohol abuse or dependence within 1 year
- Baseline ECG with a QTc interval (Bazett’s formula) >450 msec (men) and >470 msec (women) or the presence of any clinically significant cardiac abnormalities, including but not limited to patterns consistent with recent myocardial ischemia, electrolyte abnormalities, atrial or ventricular dysrhythmia or significant conduction abnormalities
- Excluded concomitant medications: any psychotropic agents (including antipsychotic, antidepressant, anxiolytic, mood stabilizer, anticonvulsant agents or agents for the treatment of Attention Deficit Disorder) with the exception of low dose benzodiazepine or hypnotic agents for the treatment of insomnia (up to 2 mg lorazepam/day or equivalent dose of a benzodiazepine or hypnotic agent); any anorectic or weight loss agents; any over-the-counter dietary supplements or herbs with psychoactive, appetite or weight effects; alpha-adrenergic blockers; dopamine agonists; clonidine; coumadin; theophylline; cimetidine; oral corticosteroids; cholestyramine, cholestypol, Depo-Provera®; smoking cessation agents; use of opioid or opioid-like medications, including analgesics and antitussives**.**
- History of surgical or device (e.g., gastric banding) intervention for obesity
- History of seizures of any etiology, or of predisposition to seizures (e.g., history of cerebrovascular accident, head trauma with ≥5 minutes loss of consciousness, concussion symptoms lasting ≥15 minutes, brain surgery, skull fracture, subdural hematoma, or febrile seizures)
- History of treatment with bupropion or naltrexone within the preceding 12 months

- History of hypersensitivity or intolerance to bupropion or naltrexone
- Change in smoking status or in tobacco or nicotine use in the previous 3 months or planned during study participation.
- Participation in a weight loss management program within one month prior to randomization
- Pregnant or breast-feeding women or planning to become pregnant during the study period or within 30 days of discontinuing study drug
- Planned surgical procedure that can impact the conduct of the study
- Use of investigational drug, device or procedure within previous 30 days.
- Participation in any previous clinical trial sponsored by Orexigen Therapeutics
- Any condition which in the opinion of the investigator makes the subject unsuitable for inclusion in this study

Supplementary Table 2. Changes in markers of glycemic control from baseline to endpoint, with last observation prior to alteration of OAD carried forward.

	Placebo (N=159)	NB (N=265)	P-value
HbA1c, %†			
Baseline	8.0±0.9	7.9±0.8	
Change	+0.1±0.1	-0.6±0.1	<0.001
Fasting blood glucose, mg/dL†			
Baseline	164.1±44.9	160.0±41.6	
Change	+2.4±3.5	-15.0±2.8	<0.001
Fasting insulin, µIU/mL††			
Baseline	14.1	15.0	
Percent change (95% CI)	-10.2% (-19.7%, 0.5%)	-16.0% (-22.6%, -8.8%)	0.330
HOMA-IR††			
Baseline	5.2	5.6	
Percent change (95% CI)	-9.4% (-21.7%, -4.9%)	-23.3% (-31.2%, -14.5%)	0.065

Change from baseline to last post-baseline observation prior to rescue medication on study drug. mITT-LOCF population. Baseline values are mean±SD (†) or geometric mean (††); change data are LS mean±SE change from baseline (†), or LS % change from baseline with 95% confidence intervals (†). P values are nominal (i.e. not adjusted for multiple comparisons) and associated with exploratory treatment comparisons.

SUPPLEMENTARY DATA

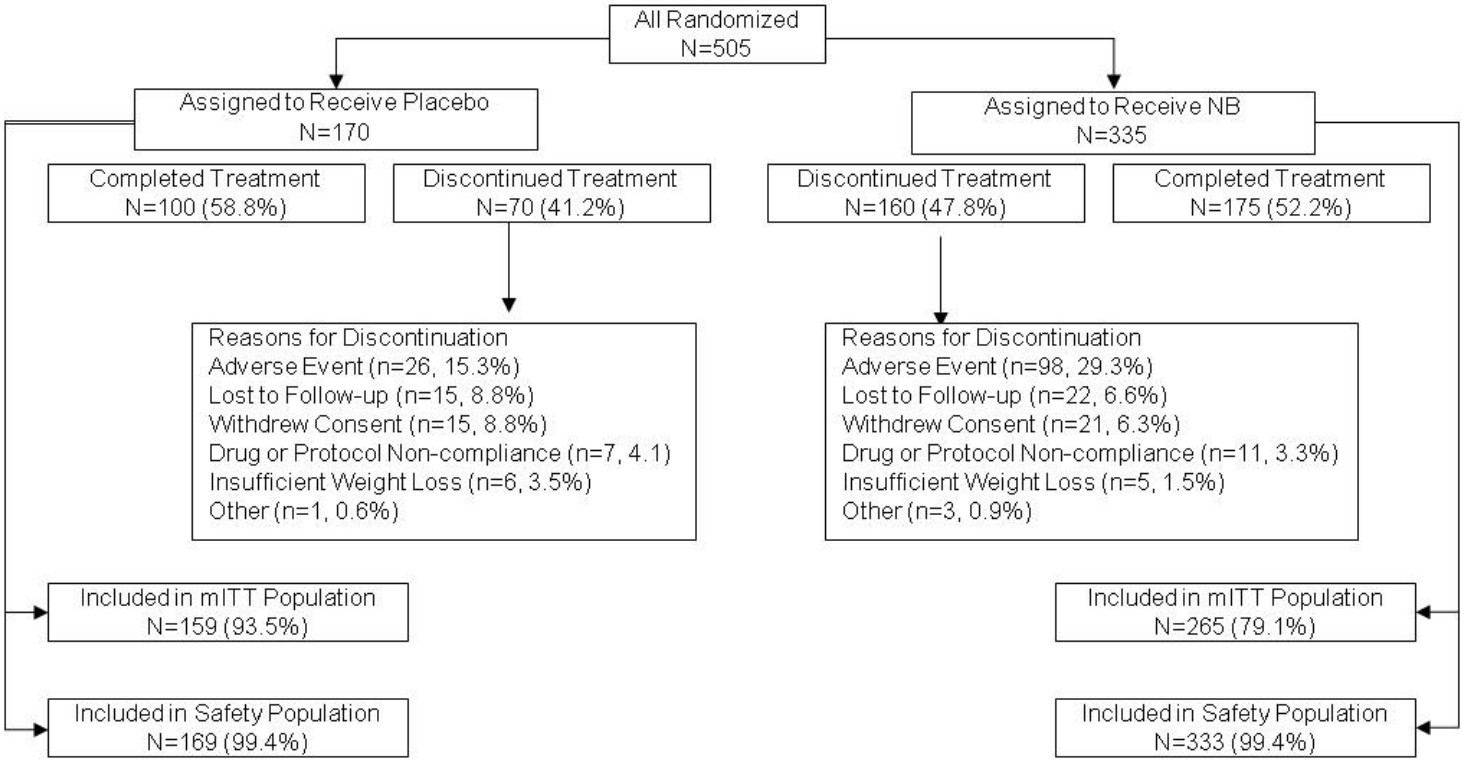
Supplementary Table 3. Systolic / Diastolic Blood Pressure and Pulse Rate Outlier Analysis.

	Placebo (N=169) n (%)	NB32 (N=333) n (%)
Patients with ≥1 postbaseline measurement reported	161	293
Blood Pressure		
Patients with ≥2 consecutive values above baseline[1]		
Systolic ≥10 mm Hg increase	42 (26.1%)	85 (29.0%)
Diastolic ≥5 mm Hg increase	52 (32.3%)	109 (37.2%)
Patients with ≥2 consecutive values above respective systolic/diastolic threshold[1,2]		
Systolic ≥160 mm Hg	1 (0.6%)	3 (1.0%)
Diastolic ≥100 mm Hg	1 (0.6%)	3 (1.0%)
Pulse Rate		
Patients with ≥2 consecutive values above baseline[1]		
≥5 bpm increase	76 (47.2%)	147 (50.2%)
≥10 bpm increase	35 (21.7%)	68 (23.2%)
Patients with ≥2 consecutive values above pulse rate threshold of ≥90 bpm [1,2]	9 (5.6%)	18 (6.1%)

[1]Or single measurement above threshold if final measurement.
[2]Patients with value above stated threshold at baseline were excluded from analysis.

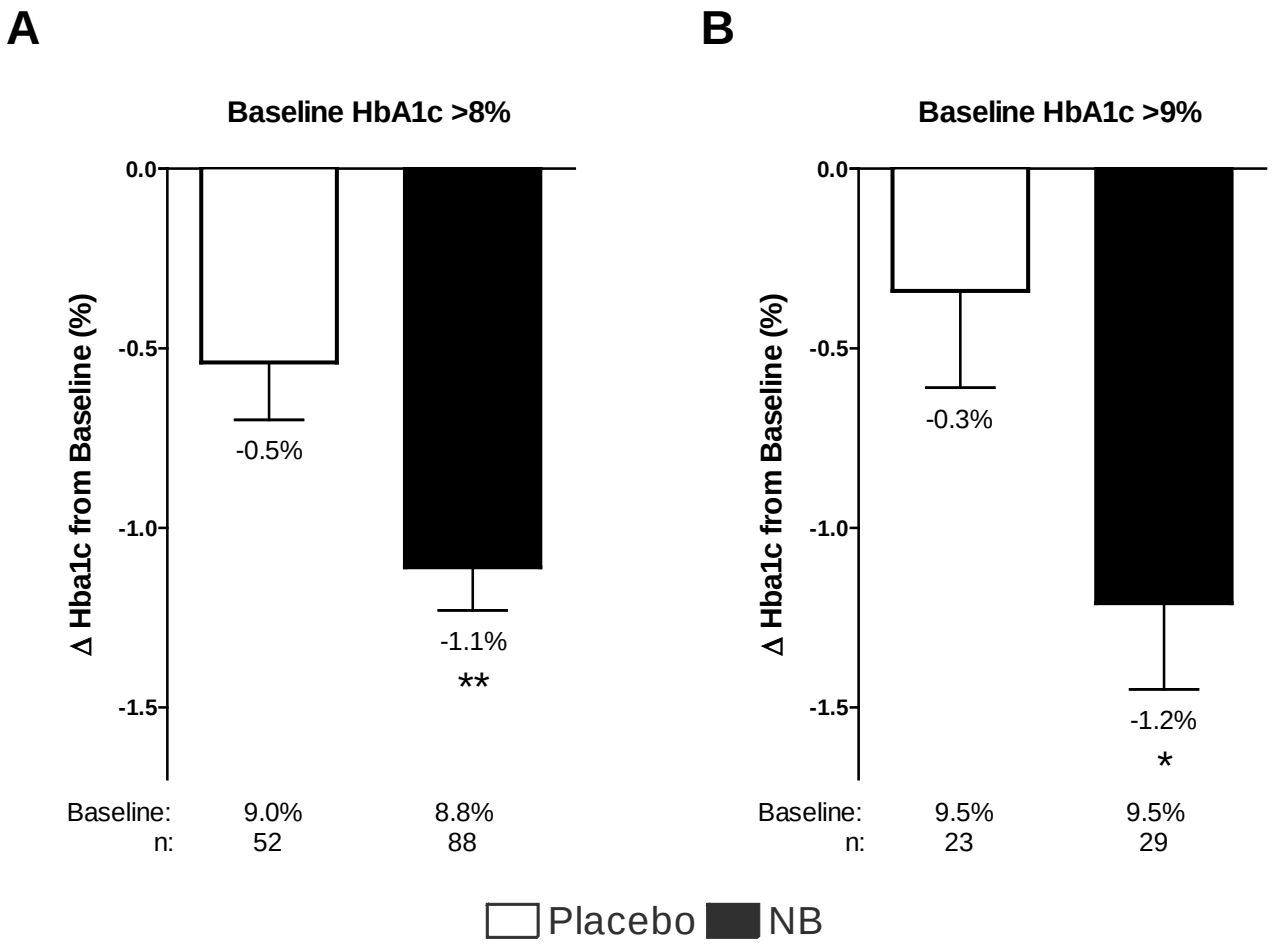
SUPPLEMENTARY DATA

Supplementary Figure 1. Consort Diagram.



SUPPLEMENTARY DATA

Supplementary Figure 2. Change in HbA1c in patients with baseline HbA1c >8%(A) and 9% (B).



Data are LS mean±SE; Change from baseline to Week 56 endpoint; mITT-LOCF population.**P<0.01, *P<0.05 vs. Placebo; P values are nominal (i.e. not adjusted for multiple comparisons) and associated with exploratory analyses.