Original Investigation

Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors
A Randomized Clinical Trial

Steven E. Nissen, MD; Kathy E. Wolski, MPH; Lisa Prcela, RN; Thomas Wadden, PhD; John B. Buse, MD, PhD; George Bakris, MD; Alfonso Perez, MD; Steven R. Smith, MD

IMPORTANCE Few cardiovascular outcomes trials have been conducted for obesity treatments. Withdrawal of 2 marketed drugs has resulted in controversy about the cardiovascular safety of obesity agents.

OBJECTIVE To determine whether the combination of naltrexone and bupropion increases major adverse cardiovascular events (MACE, defined as cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction) compared with placebo in overweight and obese patients.

DESIGN, SETTING, AND PARTICIPANTS Randomized, multicenter, placebo-controlled, double-blind noninferiority trial enrolling 8910 overweight or obese patients at increased cardiovascular risk from June 13, 2012, to January 21, 2013, at 266 US centers. After public release of confidential interim data by the sponsor, the academic leadership of the study recommended termination of the trial and the sponsor agreed.

INTERVENTIONS An Internet-based weight management program was provided to all participants. Participants were randomized to receive placebo (n=4454) or naltrexone, 32 mg/d, and bupropion, 360 mg/d (n=4456).

MAIN OUTCOMES AND MEASURES Time from randomization to first confirmed occurrence of a MACE. The primary analysis planned to assess a noninferiority hazard ratio (HR) of 1.4 after 378 expected events, with a confidential interim analysis after approximately 87 events (25% interim analysis) to assess a noninferiority HR of 2.0 for consideration of regulatory approval.

RESULTS Among the 8910 participants randomized, mean age was 61.0 years (SD, 7.3 years), 54.5% were female, 32.1% had a history of cardiovascular disease, and 85.2% had diabetes, with a median body mass index of 36.6 (interquartile range, 33.1-40.9). For the 25% interim analysis, MACE occurred in 59 placebo-treated patients (1.3%) and 35 naltrexone-bupropion–treated patients (0.8%; HR, 0.59; 95% CI, 0.39-0.90). After 50% of planned events, MACE occurred in 102 patients (2.3%) in the placebo group and 90 patients (2.0%) in the naltrexone-bupropion group (HR, 0.88; adjusted 99.7% CI, 0.57-1.34). Adverse effects were more common in the naltrexone-bupropion group, including gastrointestinal events in 14.2% vs 1.9% ($P < .001$) and central nervous system symptoms in 5.1% vs 1.2% ($P < .001$).

CONCLUSIONS AND RELEVANCE Among overweight or obese patients at increased cardiovascular risk, based on the interim analyses performed after 25% and 50% of planned events, the upper limit of the 95% CI of the HR for MACE for naltrexone-bupropion treatment, compared with placebo, did not exceed 2.0. However, because of the unanticipated early termination of the trial, it is not possible to assess noninferiority for the prespecified upper limit of 1.4. Accordingly, the cardiovascular safety of this treatment remains uncertain and will require evaluation in a new adequately powered outcome trial.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01601704

JAMA. 2016;315(10):990-1004. doi:10.1001/jama.2016.1558

Editorial page 984

Related article page 1046

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com

Author Affiliations: Cleveland Clinic Center for Cardiovascular Research, Cleveland, Ohio (Nissen, Wolski, Prcela); Center for Weight and Eating Disorders Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia (Wadden); University of North Carolina School of Medicine, Chapel Hill (Buse); ASH Comprehensive Hypertension Center, University of Chicago Medicine, Chicago, Illinois (Bakris); Takeda Pharmaceuticals, Deerfield, Illinois (Perez); Translational Research Institute for Metabolism and Diabetes, Florida Hospital, Sanford-Burnham Medical Research Institute, Orlando (Smith).

Corresponding Author: Steven E. Nissen, MD, Cleveland Clinic, 8500 Euclid Ave, Cleveland, OH 44195 (nissens@ccf.org).

The prevalence of obesity has increased steadily in the United States and globally over the last several decades, and this disorder is now considered one of the most serious contemporary threats to cardiovascular health.[1] The current obesity epidemic has resulted in a substantial increase in the incidence of diabetes mellitus and related complications.[2] Lifestyle modification has long been considered a mainstay of therapy for obesity, but this intervention has produced only modest weight loss and no reduction in major adverse cardiovascular events (MACE).[3] Accordingly, treatment strategies have centered on pharmacological and surgical approaches to weight reduction. Drug treatments for obesity have yielded mixed results, with pharmacological agents achieving modest weight loss but without demonstrating a reduction in cardiovascular events. Two therapies, fenfluramine and sibutramine, were removed from the market after evidence of cardiovascular harm emerged.[4,5] Accordingly, the medical community and regulatory authorities have expressed concerned about the cardiovascular safety of new drugs to treat obesity.

The combination of naltrexone and bupropion reduced weight during phase 3 clinical trials,[6] but the US Food and Drug Administration (FDA) deferred approval based on safety concerns related to small increases in blood pressure and heart rate in these trials.[7] The FDA mandated a placebo-controlled, noninferiority cardiovascular outcomes trial, specifying that an interim analysis after 25% of expected events had accrued would need to rule out an upper 95% confidence interval of the hazard ratio (HR) of 2.0 prior to approval and a HR of 1.4 at study completion (potentially postapproval).[8] Both the sponsor and the FDA agreed to not disclose the 25% interim analysis until completion of the study. While the trial was ongoing, the sponsor publicly released the confidential 25% interim results via a patent publication.[9] The study's academic leadership recommended termination of the trial due to the breach of confidentiality and the sponsor agreed. The current report provides results for the 50% interim data, which was the last prespecified analysis performed by the data monitoring committee prior to public disclosure. We also include the 25% interim analysis and a sensitivity analysis based on the final data available at last patient contact.

Methods

Study Design

The study was a phase 3b, multicenter, randomized, double-blind, placebo-controlled trial to assess the occurrence of MACE in overweight or obese patients at increased risk of adverse cardiovascular outcomes treated with an extended-release, fixed-dose formulation containing a total daily dose of 32 mg of naltrexone and 360 mg of bupropion. Interim monitoring boundaries allowed for early termination for either superior efficacy or established harm but not based on noninferiority considerations.

The study enrolled patients into a double-blind lead-in period to identify patients who did not tolerate treatment with low-dose naltrexone-bupropion or who exhibited poor adherence. During the lead-in period, participants were randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences: 1 week of active study medication followed by 1 week of placebo or 1 week of placebo followed by 1 week of active study medication. Eligible patients were subsequently randomized to treatment with either naltrexone-bupropion or placebo in a 1:1 ratio (**Figure 1**). Randomization occurred via an interactive voice recognition system using a permuted block size of 4 with no stratification factors. To achieve the requisite number of events, the duration of randomized treatment was estimated to be between 2 and 4 years.

The trial required discontinuation from study medication at week 16 in a blinded manner for patients who did not lose 2% or more of their initial body weight or experienced a sustained (at ≥2 visits) increase in blood pressure (systolic or diastolic) of 10 mm Hg or greater. The approach was selected in consultation with the FDA to avoid administration of naltrexone-bupropion to patients who did not lose weight or who experienced clinically unacceptable increases in blood pressure as suggested in the labeling for bupropion.

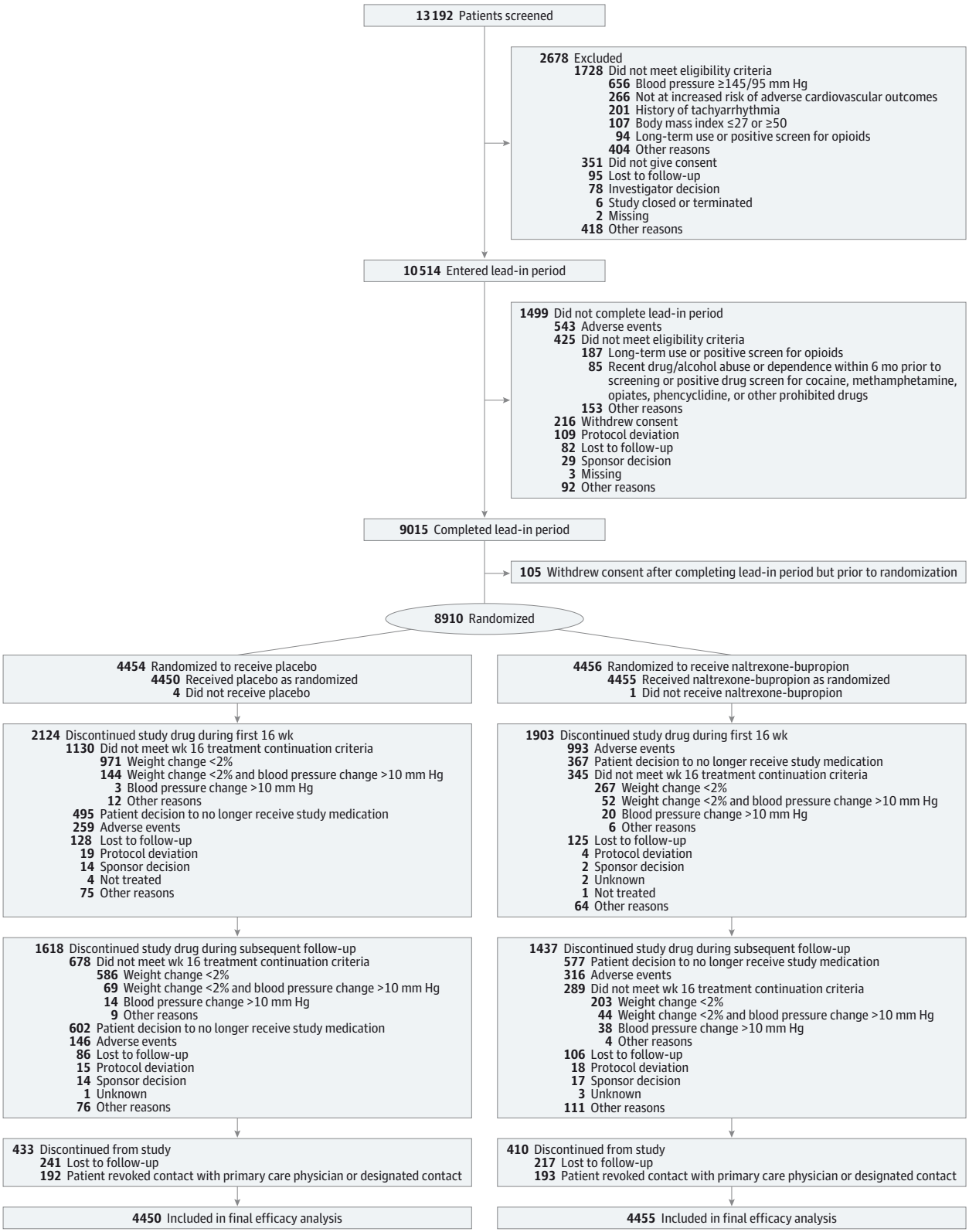
Study Population

The study was approved by an institutional review board for all study sites, and all enrolled patients provided written informed consent. Overweight or obese patients at increased risk of adverse cardiovascular outcomes were eligible to participate in the trial. The study required eligible patients to be aged 50 years or older (women) or 45 years or older (men), have a body mass index between 27 and 50 (calculated as weight in kilograms divided by height in meters squared), and have a waist circumference of 88 cm or more (women) or 102 cm or more (men). Enrollment was restricted to patients with characteristics associated with an increased risk of adverse cardiovascular outcomes.

Several categories of increased risk were prespecified, including documented preexisting cardiovascular disease. Patients could also be enrolled if they demonstrated angina with an abnormal graded exercise test result or exercise cardiac imaging study (echocardiography or nuclear scintigraphy); an ankle brachial index of less than 0.9; or documented 50% or greater stenosis of a coronary, carotid, or lower extremity artery. Patients with type 2 diabetes mellitus were eligible if they had 2 or more of the following: hypertension, dyslipidemia requiring pharmacotherapy, low high-density lipoprotein cholesterol (<50 mg/dL [1.30 mmol/L] in women or <40 mg/dL [1.04 mmol/L] in men), or current tobacco smoking. Patients were required to have consistent access to broadband Internet.

Patients were excluded for a myocardial infarction within 3 months prior to screening, severe angina pectoris, New York Heart Association class 3 or 4 heart failure, or history of stroke or blood pressure of 145/95 mm Hg or higher. Patients were also excluded for unstable weight within 3 months prior to screening (weight gain or loss of >3%), planned bariatric or cardiac surgery, or percutaneous coronary intervention. Other key exclusion criteria were severe renal impairment (estimated glomerular filtration rate <30 mL/min), elevated liver enzymes more than 3 times the

Figure 1. Flow of Participants Through the Trial



upper limit of normal, long-term opioid use, history of seizures or cranial trauma, mania, bulimia, anorexia nervosa, acute depressive illness, or suicidality. Patients taking monoamine oxidase inhibitors within 14 days prior to screening were excluded. Race/ethnicity was assessed by the investigator; this information was collected to determine if there were differences in outcomes for patients with different racial or ethnic backgrounds.

Treatments

All patients were encouraged to participate in an Internet-based weight management program that included educational resources on healthy eating, exercise, and behavioral modifications. Program information was presented in the form of weekly lessons that the study participants could access online, and they also received weekly emails with healthy lifestyle tips and reminders. Patients also had access to a personal weight loss coach; programs to track weight, meals, and physical activity; and a low-fat, low-calorie meal plan.

Patients who discontinued study medication prematurely were encouraged to continue the weight management program. The study medication (naltrexone-bupropion or placebo) was provided in tablet form. Each active tablet contained an extended-release formulation of 8 mg of naltrexone and 90 mg of bupropion or placebo. All tablets were identical in appearance. Dose escalation occurred during the first 4 weeks of treatment, beginning with 1 tablet daily during the first week, increasing to 2 tablets during week 2, 3 tablets during week 3, and 4 tablets daily during week 4 and thereafter. Dosage levels requiring more than 1 tablet daily were administered twice per day (morning and evening).

Outcome Measures

A blinded independent clinical events committee at the Cleveland Clinic Center for Clinical Research adjudicated clinical outcomes, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and all-cause mortality. The prespecified primary outcome measure was time from treatment randomization to the first confirmed occurrence of a MACE, defined as cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. The prespecified secondary outcomes were times to first occurrence of MACE or hospitalization for unstable angina, fatal or nonfatal stroke, and fatal or nonfatal myocardial infarction. The incidence of coronary revascularization was collected but not adjudicated. Additional outcome measures included changes in body weight, body mass index, and waist circumference. Although not prespecified in the protocol, time-weighted changes in blood pressure and heart rate over the course of the trial were assessed. Changes were also determined after 16 weeks of treatment, when adherence was relatively high, to assess the peak effects of naltrexone-bupropion on these vital signs.

Statistical Analysis

The protocol specified enrollment of approximately 9880 patients into the double-blind lead-in period, with the anticipation that 8900 would be randomized into the double-blind treatment period. The primary analyses were performed for the intention-to-treat (ITT) population, defined as patients who underwent randomization into the treatment period and were dispensed study medication. No imputation was performed for missing data. Analyses were also performed for an "on-treatment" population, defined as ITT patients who took at least 1 dose of study medication, with censoring of events occurring more than 30 days after a patient's last confirmed dose of study medication.

For the primary end point, 3 null hypotheses were prespecified: (1) that the HR for naltrexone-bupropion relative to placebo is 2.0 or greater; (2) that the HR for naltrexone-bupropion relative to placebo is 1.4 or greater; and (3) that the HR for naltrexone-bupropion relative to placebo is 1.0 or greater (test for superiority). Estimates of the HRs and associated confidence intervals comparing naltrexone-bupropion with placebo were obtained using the Cox proportional hazards model, with randomized treatment as a covariate and the Kaplan-Meier method used for time-to-event plots. Continuous measurements of body weight and blood pressure over time were analyzed using a general linear model with treatment, cardiovascular risk group, race, and sex as factors and with age and baseline values as covariates. Categorical data were assessed using the χ^2 test.

An initial noninferiority analysis was planned after accrual of approximately 87 events (25% interim analysis) to determine whether a 2-tailed upper bound of the 95% confidence interval of the HR would rule out 2.0 (testing null hypothesis 1), in which 1.31 was the least favorable HR point estimate consistent with this noninferiority boundary. The study design mandated that the 25% interim analysis be provided exclusively to a core team from the sponsor to enable regulatory filing for approval, but all personnel involved in the ongoing trial would remain blinded to these results. The FDA agreed to keep the interim results confidential until the trial was completed.

Sequential monitoring for superior efficacy or harm (testing null hypothesis 3) was performed by the data monitoring committee using O'Brien-Fleming group sequential boundaries, implemented using a Lan-DeMets α spending function with planned interim analyses at 50% and 75% of event accrual.[10] The primary analysis of the study would be formally addressed only after accrual of 378 events (at study completion) to determine whether an upper bound of the 95.6% confidence interval of the HR would rule out 1.4 (testing null hypothesis 2), in which the least favorable HR point estimate consistent with noninferiority was 1.14.

The study design did not allow prematurely stopping the trial for achievement of the prespecified noninferiority criterion (HR ≤1.4) prior to study completion. The 50% interim and final results were analyzed using 99.7% confidence intervals based on the prespecified α spending function for testing null hypothesis 3 after 192 adjudicated MACE.[10] The 25% interim results were analyzed using the 95% confidence intervals as prespecified in the protocol (Supplement) and statistical analysis plan. As a sensitivity analysis, MACE outcomes were also reported at the time of last patient contact (after approximately 64% of planned events had accrued). No *P* values for

noninferiority are reported because these cannot be appropriately adjusted for data derived from interim analyses not intended to serve as evidence for achievement of the prespecified criterion for noninferiority. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc).

Sample Size Determination

The trial was designed to provide 90% power to rule out the 1.4 margin (ie, the upper limit of the confidence interval would not exceed 1.4) when the true HR is 1.0, which required 378 primary events. The early preapproval analysis to rule out the 2.0 margin required 87 primary events to provide 90% power when the true HR is 1.0. In both settings, a 1-sided type I error (α) of 2.5% was used. To obtain sample sizes, an annualized rate of primary events of 1.5% in the placebo group was assumed. The recruitment was assumed to take 1.5 years, with maximum patient follow-up of 4 years. It was assumed that 7% of the study population would discontinue during the lead-in period, with a loss-to-follow-up rate of 1.2% annually. Under these assumptions, the trial required 3448 participants per treatment group. However, the study planned to recruit 4450 per treatment group to compensate for any deviations from the anticipated event rate or recruitment or retention rates.

Early Data Release and Study Termination

The study's academic executive steering committee, data monitoring committee, and sponsor at the time (Orexigen Therapeutics) developed a data access plan specifying strict confidentiality of interim data to be used in a regulatory filing for drug approval. The data monitoring committee released interim data to the sponsor after approximately 25% of planned events had accrued in November 2013, and the blinded trial continued as planned. On September 10, 2014, the FDA approved naltrexone-bupropion for marketing but publicly stated that the number of individuals who had received knowledge of the interim results, both inside and outside the company, was far greater than the agency considered essential to facilitate the regulatory submission for approval.[11] The FDA also stated that due to the breach of confidentiality, the trial could not be used to meet the postapproval requirement to rule out a noninferiority margin of 1.4.[11] Nonetheless, the FDA encouraged the sponsor to continue the trial as originally planned.

In March 2015, while the trial was still ongoing (after sponsorship was transferred to Takeda Pharmaceuticals), Orexigen publicly released the 25% interim results via a patent publication and submission to the Securities and Exchange Commission.[9] The published patent claimed a method for reducing cardiovascular risk and included the 25% interim data for MACE showing an estimated HR of 0.59, which was reported in the media as evidence of a cardiovascular benefit for naltrexone-bupropion.[12]

The executive steering committee concluded that the premature release of interim data had compromised the scientific integrity of the ongoing study, precluding successful completion. The executive steering committee recommended trial termination on May 12, 2015, and the original sponsor (Orexigen Therapeutics) and the current holder of the Investigational New Drug application (Takeda Pharmaceuticals) agreed. The executive steering committee also decided to unblind and partially release outcome data from a recently completed, preplanned 50% interim analysis to correct the impression of benefit created by release of potentially unreliable 25% interim data.[13] The executive steering committee expressed concern that the breach of confidentiality through release of preliminary data could result in inappropriate use of naltrexone-bupropion with an expectation of cardiovascular benefit.

The 50% interim analysis was completed on March 3, 2015, based on 192 adjudicated MACE (from a database lock on February 3, 2015). As a result of the termination of the study, the preplanned 50% interim analysis was considered the most appropriate analysis to generate the primary results. Additional outcomes accumulated after the February 2015 database lock are included in a sensitivity analysis, which reports results after 64% of planned events. The 25% interim analysis used in the regulatory approval of naltrexone-bupropion is also reported.

Results

Patients

The disposition of patients is shown in Figure 1. From June 13, 2012, until January 21, 2013, the trial screened 13 192 patients and randomized 10 514 into the lead-in period, and 10 505 were included in the enrolled population (9 patients did not receive study medication), with 9015 patients (85.8%) successfully completing this phase. The most common reason for noncompletion during the lead-in was an adverse event, which occurred in 543 patients (5.2%). Ultimately, 8910 patients were randomized into the ongoing study, with 8905 included in the ITT population (5 did not receive study medication).

The baseline characteristics of the patients are shown in **Table 1**. The mean age of randomized patients was 61.0 years (SD, 7.3 years), with a slight predominance of women (54.5%), and 83.5% patients were described as white. The median body mass index was 36.6 (interquartile range [IQR], 33.1-40.9), with a median body weight of 104.1 kg (IQR, 92.1-118.1 kg) and a median waist circumference of 118.1 cm (IQR, 110-128 cm). Type 2 diabetes was present in 85.2% of patients, established cardiovascular disease in 32.1%, and both disorders in 17.4%. Cardiovascular risk factors were well controlled, with a mean systolic blood pressure of 125.7 mm Hg (SD, 12.5 mm Hg), a median low-density lipoprotein cholesterol level of 82.0 mg/dL (2.12 mmol/L) (IQR, 65-106 mg/dL [1.68-2.75 mmol/L]), and a median high-density lipoprotein cholesterol level of 45.0 mg/dL (1.17 mmol/L) (IQR, 38-53 mg/dL [0.98-1.37 mmol/L]). Concomitant medications included statins in 79.2% of patients, antihypertensive medications in 92.0%, and glucose-lowering agents in 75.1%.

Efficacy Outcomes

Primary End Point

Table 2 shows the primary and secondary cardiovascular outcomes for the ITT population at the 50% interim analysis. The

primary prespecified outcome measure, time to first MACE, occurred in 192 patients, 102 (2.3%) in the placebo group and 90 (2.0%) in the naltrexone-bupropion group (HR, 0.88; 99.7% CI, 0.57-1.34). The components of the primary composite outcome included cardiovascular death in 34 placebo-treated patients (0.8%) and 17 naltrexone-bupropion-treated patients (0.4%; HR, 0.50; 99.7% CI, 0.21-1.19). Nonfatal stroke occurred in 19 patients (0.4%) in the placebo group and 21 (0.5%) in the naltrexone-bupropion group (HR, 1.10; 99.7% CI, 0.44-2.78). Nonfatal myocardial infarction occurred in 54 patients (1.2%) in the placebo group and 54 (1.2%) in the naltrexone-bupropion group (HR, 1.00; 99.7% CI, 0.57-1.75). **Figure 2**A shows the Kaplan-Meier plot of time to first MACE for the 50% interim analysis.

Table 3 shows results of the sensitivity analysis based on the final end-of-study assessment for the primary and secondary cardiovascular outcomes in the ITT population. The primary outcome measure, time to first MACE, occurred in 124 patients (2.8%) in the placebo treatment group and 119 patients (2.7%) in the naltrexone-bupropion group (HR, 0.95; 99.7% CI, 0.65-1.38). The components of the primary composite outcome showed cardiovascular death in 42 placebo-treated patients (0.9%) and 26 naltrexone-bupropion-treated patients (0.6%; HR, 0.61; 99.7% CI, 0.30-1.27). Nonfatal stroke occurred in 21 patients (0.5%) in the placebo group and 28 (0.6%) in the naltrexone-bupropion group (HR, 1.32; 99.7% CI, 0.57-3.08). Nonfatal myocardial infarction occurred in 67 patients (1.5%) in the placebo group and 68 (1.5%) in the naltrexone-bupropion group (HR, 1.01; 99.7% CI, 0.61-1.66). Figure 2B shows the Kaplan-Meier plot of time to first MACE for the final end-of-study analysis.

Table 4 shows the results from the 25% interim analysis used in the regulatory approval of naltrexone-bupropion and subsequently released by the original sponsor (Orexigen) in a patent filing. The primary outcome, time to first MACE, occurred in 59 patients (1.3%) in the placebo group and 35 patients (0.8%) in the naltrexone-bupropion group (HR, 0.59; 95% CI, 0.39-0.90). Table 4 also shows events rates and HRs with 95% confidence intervals for components of the primary outcome and secondary outcomes for the 25% interim analysis. The 25% interim analysis shows 95% confidence intervals rather than 99.7% confidence intervals because this analysis tested only whether the trial ruled out a noninferiority margin of 2.0 and did not test for the margin of 1.4. Table 4 also shows the primary end point and its components for the on-treatment analysis. For the on-treatment analyses, the HRs are less favorable than the ITT analyses and show wider confidence intervals.

Secondary Outcomes

Table 2 shows the secondary outcome measures for the ITT population at the 50% interim analysis. The composite of MACE plus hospitalization for unstable angina occurred in 142 placebo patients (3.2%) and 133 naltrexone-bupropion-treated patients (3.0%; HR, 0.93; 99.7% CI, 0.66-1.33). Table 3 shows these same outcomes at study completion and Table 4 shows these outcomes for the 25% interim analysis. Results at study completion (64% of planned events) were less favorable than observed at the 50% interim analysis (HR, 0.95; 99.7% CI, 0.95-1.38). The 25% interim analysis showed more favorable HRs than subsequent analyses, with very wide confidence intervals due to the low number of events. Table 2, Table 3, and

Table 1. Demographics and Baseline Characteristics of the Intention-to-Treat Population

Characteristics	Placebo (n = 4450)	Naltrexone-Bupropion (n = 4455)
Demographics and laboratory characteristics		
Age, mean (SD), y	60.9 (7.38)	61.1 (7.27)
Female, No. (%)	2419 (54.4)	2437 (54.7)
White, No. (%)	3698 (83.1)	3738 (83.9)
Blood pressure, mean (SD), mm Hg		
Systolic	125.5 (12.6)	125.9 (12.5)
Diastolic	74.4 (9.1)	74.5 (9.0)
Weight, mean (SD), kg	106.3 (19.2)	105.6 (19.1)
Body mass index, median (IQR)[a]	36.7 (33.1-41.1)	36.6 (33.1-40.8)
Waist circumference, median (IQR), cm	118.5 (110-128)	118.0 (110-128)
Glycohemoglobin level in patients with diabetes, median (IQR), %	7.1 (6.4-8.2)	7.0 (6.1-8.1)
Cholesterol, median (IQR), mg/dL		
Low-density lipoprotein	82.0 (65-106)	82.0 (64-105)
High-density lipoprotein	45.0 (38-54)	45.0 (37-53)
Triglycerides, median (IQR), mg/dL	166.0 (120-230)	166.0 (119-232)
High-sensitivity C-reactive protein, median (IQR), mg/L	2.9 (1.4-5.9)	2.9 (1.4-5.9)
Cardiovascular risk factors, No. (%)		
Cardiovascular disease	1447 (32.5)	1415 (31.8)
Type 2 diabetes mellitus	3803 (85.5)	3784 (84.9)
Duration of type 2 diabetes mellitus, median (IQR), y	7.6 (3.8-12.9)	7.8 (3.9-12.9)
Cardiovascular disease and type 2 diabetes mellitus	801 (18.0)	745 (16.7)
Current smoker	416 (9.3)	405 (9.1)
Hypertension	4117 (92.5)	4162 (93.4)
Dyslipidemia	4070 (91.5)	4100 (92.0)
Medications, No. (%)		
Statin	3518 (79.1)	3534 (79.3)
Insulin	1038 (23.3)	1038 (23.3)
Metformin	2543 (57.1)	2525 (56.7)
β-Blocker	1705 (38.3)	1768 (39.7)
Diuretic	1413 (31.8)	1470 (33.0)
ACE inhibitor or ARB	3407 (76.6)	3440 (77.2)
Calcium channel blocker	845 (19.0)	905 (20.3)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range.

SI conversions: To convert low- and high-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259. To convert triglycerides to millimoles per liter, multiply by 0.0113.

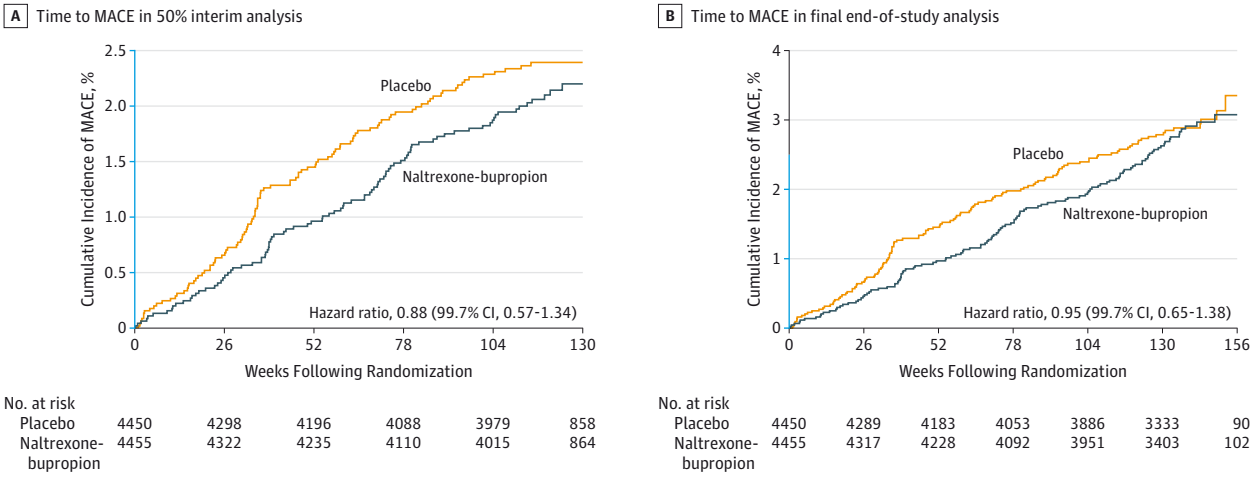
[a] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Primary and Secondary Efficacy Outcomes (50% Interim Analysis)

End Points	Placebo, No. (%) (n = 4450)	Naltrexone-Bupropion, No. (%) (n = 4455)	Hazard Ratio (99.7% CI)[a]
Intention-to-treat analysis			
Primary outcome			
Major adverse cardiovascular events	102 (2.3)	90 (2.0)	0.88 (0.57-1.34)
Components of the primary outcome			
Cardiovascular death	34 (0.8)	17 (0.4)	0.50 (0.21-1.19)
Nonfatal stroke	19 (0.4)	21 (0.5)	1.10 (0.44-2.78)
Nonfatal myocardial infarction	54 (1.2)	54 (1.2)	1.00 (0.57-1.75)
Secondary outcomes			
Major adverse cardiovascular events + hospitalization for unstable angina	142 (3.2)	133 (3.0)	0.93 (0.66-1.33)
Fatal or nonfatal stroke	21 (0.5)	22 (0.5)	1.04 (0.43-2.55)
Fatal or nonfatal myocardial infarction	57 (1.3)	55 (1.2)	0.96 (0.55-1.67)
Other outcomes			
All-cause mortality	51 (1.1)	43 (1.0)	0.84 (0.46-1.54)
Hospitalization for unstable angina	43 (1.0)	47 (1.1)	1.09 (0.59-2.02)
Coronary revascularization	145 (3.3)	132 (3.0)	0.91 (0.64-1.29)
All-cause mortality plus nonfatal myocardial infarction + nonfatal stroke	119 (2.7)	114 (2.6)	0.95 (0.65-1.40)
Major adverse cardiovascular events + hospitalization for unstable angina + coronary revascularization	205 (4.6)	188 (4.2)	0.91 (0.68-1.23)
On-treatment analysis			
Major adverse cardiovascular events	37 (0.8)	43 (1.0)	0.97 (0.50-1.88)
Components of the primary outcome			
Cardiovascular death	10 (0.2)	8 (0.2)	0.67 (0.17-2.72)
Nonfatal stroke	7 (0.2)	11 (0.2)	1.25 (0.30-5.18)
Nonfatal myocardial infarction	21 (0.5)	24 (0.5)	0.96 (0.40-2.3)

[a] Based on Cox proportional hazards model with treatment as a factor; adjusted 99.7% CIs based on group sequential design.

Figure 2. Time to MACE in the 50% Interim Analysis and the Final End-of-Study Analysis



MACE indicates major adverse cardiovascular events. Segment of y-axes shown in blue is the range of 0% to 2.5%.

Table 4 also show the additional secondary outcomes of fatal or nonfatal stroke and fatal or nonfatal myocardial infarction for the 50% interim analysis, end-of-study analysis, and 25% interim analysis, respectively.

Other Cardiovascular Outcomes

Table 2 and Table 3 show other cardiovascular outcomes including all-cause mortality, coronary revascularization, hospitalization for unstable angina, and additional composite

Table 3. Primary and Secondary Efficacy Outcomes (Final End-of-Study Analysis)

End Points	Placebo, No. (%) (n = 4450)	Naltrexone-Bupropion, No. (%) (n = 4455)	Hazard Ratio (99.7% CI)[a]
Intention-to-treat analysis			
Primary outcome			
Major adverse cardiovascular events	124 (2.8)	119 (2.7)	0.95 (0.65-1.38)
Components of the primary outcome			
Cardiovascular death	42 (0.9)	26 (0.6)	0.61 (0.30-1.27)
Nonfatal stroke	21 (0.5)	28 (0.6)	1.32 (0.57-3.08)
Nonfatal myocardial infarction	67 (1.5)	68 (1.5)	1.01 (0.61-1.66)
Secondary outcomes			
Major adverse cardiovascular events + hospitalization for unstable angina	171 (3.8)	164 (3.7)	0.95 (0.69-1.31)
Fatal or nonfatal stroke	23 (0.5)	31 (0.7)	1.34 (0.60-2.99)
Fatal or nonfatal myocardial infarction	71 (1.6)	69 (1.5)	0.96 (0.59-1.58)
Other outcomes			
All-cause mortality	71 (1.6)	65 (1.5)	0.91 (0.55-1.50)
Hospitalization for unstable angina	50 (1.1)	51 (1.1)	1.01 (0.57-1.82)
Coronary revascularization	170 (3.8)	152 (3.4)	0.89 (0.64-1.23)
All-cause mortality + nonfatal myocardial infarction + nonfatal stroke	151 (3.4)	156 (3.5)	1.02 (0.73-1.43)
Major adverse cardiovascular events + hospitalization for unstable angina + coronary revascularization	244 (5.5)	226 (5.1)	0.92 (0.70-1.20)
On-treatment analysis			
Major adverse cardiovascular events	39 (0.9)	47 (1.1)	0.99 (0.52-1.87)
Components of the primary outcome			
Cardiovascular death	11 (0.2)	9 (0.2)	0.67 (0.18-2.54)
Nonfatal stroke	7 (0.2)	12 (0.3)	1.35 (0.33-5.47)
Nonfatal myocardial infarction	22 (0.5)	26 (0.6)	0.98 (0.42-2.30)

[a] Based on Cox proportional hazards model with treatment as a factor; adjusted 99.7% CIs based on group sequential design.

end points at the 50% interim and final end-of-study analysis. At the 50% interim analysis, all-cause mortality occurred in 51 placebo patients (1.1%) and 43 naltrexone-bupropion patients (1.0%; HR, 0.84; 99.7% CI, 0.46-1.54). Hospitalization for unstable angina occurred in 43 (1.0%) of placebo-treated patients and 47 (1.1%) of naltrexone-bupropion-treated patients (HR, 1.09; 99.7% CI, 0.59-2.02). Coronary revascularization occurred in 145 (3.3%) of placebo patients and 132 (3.0%) of naltrexone-bupropion patients (HR, 0.91; 99.7% CI, 0.64-1.29).

Table 2 and Table 3 also include the post hoc composite outcome of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke, which showed less favorable HRs than the primary outcome because the fewer cardiovascular deaths were counterbalanced by an excess of noncardiovascular mortality. The broadest measure of cardiovascular outcome, MACE plus hospitalization for unstable angina or coronary revascularization, occurred in 205 placebo patients (4.6%) and 188 naltrexone-bupropion patients (4.2%; HR, 0.91; 99.7% CI, 0.68-1.23). Table 2, Table 3, and Table 4 also show the primary end point and components of the primary end point for the on-treatment analysis. Because of the low adherence rates, these analyses have fewer patient-years of follow-up, resulting in wider confidence intervals, and consistently show less favorable HRs than the ITT population.

Adherence and Retention

Figure 3 shows time to permanent study drug discontinuation for any reason. Adherence to study drug, as expected, was relatively low and showed a different pattern between the 2 treatment groups. After the first 2 weeks of treatment, 95.1% of patients treated with naltrexone-bupropion and (97.6%) of placebo patients were taking study medication. At 16 weeks, 72.1% of placebo-treated patients and 64.0% of naltrexone-bupropion-treated patients were still taking study drug ($P < .001$). One year after randomization, 26.3% of placebo patients and 37.5% of naltrexone-bupropion patients were still taking study drug ($P < .001$). Two years after randomization, only 17.3% of placebo patients and 27.0% of naltrexone-bupropion patients were still taking study drug ($P < .001$). The median duration of treatment was 16.3 weeks for placebo (IQR, 15.6-53.1 weeks) and 18.4 weeks for naltrexone-bupropion (IQR, 8.1-109.3 weeks).

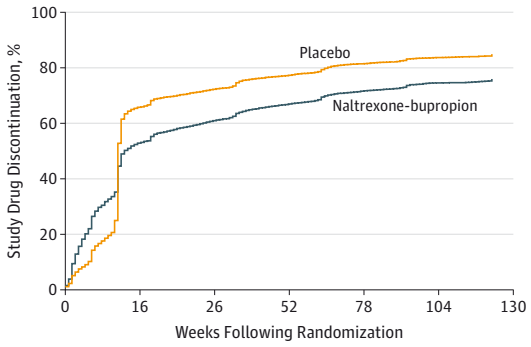
A large decrease in the number of patients receiving study drug occurred after the 16-week assessment, with 44% of placebo patients and 17.8% of naltrexone-bupropion patients discontinued by investigators. Most discontinuations were due to a failure to lose 2% of body weight, but 230 placebo patients and 154 naltrexone-bupropion patients discontinued treatment because of a greater than 10-mm Hg increase in blood pressure (Figure 1). A high percentage of patients who discon-

Table 4. Efficacy Outcomes (25% Interim Analysis)

End Points	Placebo, No. (%) (n = 4450)	Naltrexone-Bupropion, No. (%) (n = 4455)	Hazard Ratio (95% CI)[a]
Intention-to-treat analysis			
Primary outcome			
Major adverse cardiovascular events	59 (1.3)	35 (0.8)	0.59 (0.39-0.90)
Components of the primary outcome			
Cardiovascular death	19 (0.4)	5 (0.1)	0.26 (0.10-0.70)
Nonfatal stroke	10 (0.2)	7 (0.2)	0.70 (0.27-1.83)
Nonfatal myocardial infarction	33 (0.7)	23 (0.5)	0.70 (0.41-1.18)
Secondary outcomes			
Major adverse cardiovascular events + hospitalization for unstable angina	79 (1.8)	63 (1.4)	0.80 (0.57-1.11)
Fatal or nonfatal stroke	11 (0.2)	7 (0.2)	0.63 (0.25-1.64)
Fatal or nonfatal myocardial infarction	34 (0.8)	24 (0.5)	0.70 (0.42-1.19)
Other outcomes			
All-cause mortality	22 (0.5)	10 (0.2)	0.45 (0.22-0.96)
Hospitalization for unstable angina	23 (0.5)	29 (0.7)	1.26 (0.73-2.18)
Coronary revascularization	65 (1.5)	65 (1.5)	1.00 (0.71-1.41)
All-cause mortality + nonfatal myocardial infarction + nonfatal stroke	62 (1.4)	40 (0.9)	0.64 (0.43-0.96)
Major adverse cardiovascular events + hospitalization for unstable angina + coronary revascularization	105 (2.4)	91 (2.0)	0.87 (0.65-1.15)
On-treatment analysis			
Major adverse cardiovascular events	30 (0.7)	23 (0.5)	0.71 (0.41-1.22)
Components of the primary outcome			
Cardiovascular death	7 (0.2)	4 (0.1)	0.57 (0.16-1.94)
Nonfatal stroke	7 (0.2)	6 (0.1)	0.72 (0.24-2.16)
Nonfatal myocardial infarction	16 (0.4)	13 (0.3)	0.77 (0.37-1.60)

[a] Based on Cox proportional hazards model with treatment as a factor.

Figure 3. Time From Randomization to Permanent Study Drug Discontinuation



No. at risk							
Placebo	4450	2914	1465	1163	942	765	130
Naltrexone-bupropion	4455	2752	2052	1661	1394	1196	231

tinued treatment remained in follow-up for MACE and contributed to the ITT analysis. Discontinuation of follow-up occurred in 9.7% of placebo patients and 9.2% of naltrexone-bupropion patients. The median duration of follow-up was 121 weeks (IQR, 114-128 weeks) for placebo and 121 weeks (IQR, 114-128 weeks) for naltrexone-bupropion.

Other Outcome Measures

At trial completion, body weight decreased a mean of 3.9 kg (95% CI, −4.1 to −3.7 kg) in the naltrexone-bupropion group and 1.2 kg (95% CI, −1.3 to −1.0 kg) in the placebo group, corresponding to reductions of 3.6% and 1.1%, respectively ($P < .001$). The between-group mean difference was 2.7 kg (95% CI, −2.9 to −2.5 kg; $P < .001$), representing a 2.5% reduction (95% CI, −2.8% to −2.3%) in body weight. At trial completion, waist circumference decreased 2.1 cm (95% CI, −2.4 to −1.8 cm) in the naltrexone-bupropion group and 0.8 cm (95% CI, −1.0 to −0.5 cm) in the placebo group ($P < .001$). In post hoc analysis of data at 16 weeks, time-weighted systolic blood pressure increased a mean of 1.4 mm Hg (95% CI, 1.0-1.7 mm Hg) in the naltrexone-bupropion group and 0.5 mm Hg (95% CI, 0.4-0.6 mm Hg) in the placebo group ($P < .001$). Time-weighted average heart rate increased 0.7/min (95% CI, 0.5/min to 0.9/min) in the naltrexone-bupropion group and 0.6/min (95% CI, 0.3/min to 0.8/min) in the placebo group. The increase in blood pressure and heart rate at approximately 16 weeks, when adherence to treatment was still relatively high, showed a mean difference in blood pressure between treatment groups of 0.46 mm Hg (95% CI, 0.01-0.92 mm Hg) and a mean difference in heart rate of 0.45/min (95% CI, 0.11/min to 0.78/min). Plots of change over time in body weight, systolic blood pressure, and heart rate are shown in **Figure 4**, and **Figure 5**.

Adverse Events

The most common adverse events leading to the discontinuation of study drug are shown in **Table 5**. These included gastrointestinal adverse effects, which occurred in 14.2% of naltrexone-bupropion-treated patients and 1.9% of placebo-treated participants ($P < .001$), and central nervous system symptoms, which occurred in 5.1% of naltrexone-bupropion patients and 1.2% of placebo patients ($P < .001$). Psychiatric symptoms resulted in study drug discontinuation in 3.1% of naltrexone-bupropion patients and 0.9% of placebo patients ($P < .001$).

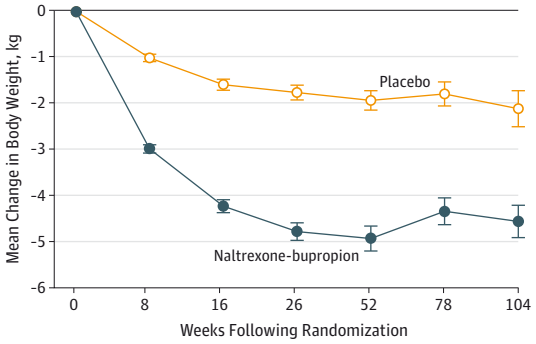
Discussion

The cardiovascular safety of obesity drugs has received considerable attention after the withdrawal of sibutramine and fenfluramine by the FDA for cardiovascular harm.[4,5] Some drugs that reduce appetite are sympathomimetic agents that can increase blood pressure and heart rate. Bupropion, a drug widely used to treat depression, has anorexigenic properties resulting in modest weight loss.[14] The effectiveness of bupropion is increased when combined with the opioid antagonist naltrexone.[15] A combination product was considered by the FDA for approval, but the agency initially rejected this new drug application because of elevation of blood pressure and heart rate, requiring a preapproval cardiovascular safety study.

Our study was designed to provide an assessment of cardiovascular outcomes for extended-release naltrexone, 32 mg/d, and bupropion, 360 mg/d. However, the study was terminated prematurely after the unplanned release of an interim analysis after 25% of planned events with MACE occurring in 59 placebo-treated patients (1.3%) and 35 naltrexone-bupropion–treated patients (0.8%; HR, 0.59; 95% CI, 0.39-0.90). After 50% of planned events, outcomes were less favorable, with MACE occurring in 102 patients (2.3%) in the placebo group and 90 patients (2.0%) in the naltrexone-bupropion group (HR, 0.88; adjusted 99.7% CI, 0.57-1.34). Given the unplanned early termination of the trial, which directly resulted from the inappropriate release of the highly favorable 25% interim data, these findings do not establish noninferiority for the prespecified margin of 1.4.

Recently, the FDA has adopted a 2-stage approach to drug approval with the intent of ruling out a high degree of hazard prior to approval based on an interim analysis of preliminary clinical trial results. These trials then continue to potentially rule out a more stringent noninferiority margin in the postapproval setting.[16] The approach of a 2-stage safety trial was originally developed to facilitate safety assessment of diabetes drugs.[16] For naltrexone-bupropion, the FDA required that the sponsor conduct a noninferiority cardiovascular outcomes trial, specifying that an interim analysis would need to rule out a noninferiority margin of 2.0 prior to approval and a margin of 1.4 at study completion (potentially postapproval).

Figure 4. Change in Body Weight During the Trial

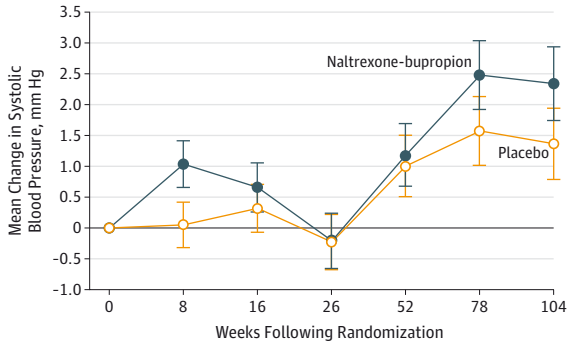


No. of patients							
Placebo	4450	4042	3738	3297	2848	2507	2264
Naltrexone-bupropion	4455	3977	3677	3404	2995	2690	2408

Error bars indicate 95% confidence intervals.

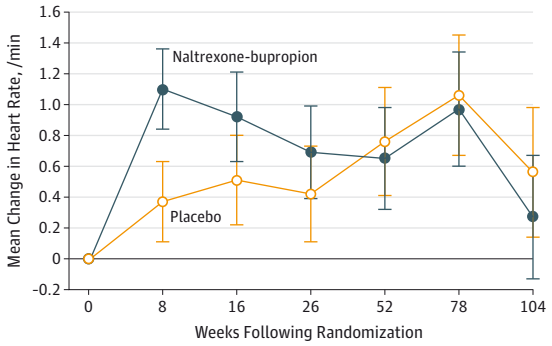
Figure 5. Changes in Systolic Blood Pressure and Heart Rate During the Trial

A Change in systolic blood pressure



No. of patients							
Placebo	4450	4042	3854	3297	2850	2506	2267
Naltrexone-bupropion	4455	3977	3871	3404	2997	2690	2409

B Change in heart rate



No. of patients							
Placebo	4450	4042	3854	3297	2850	2506	2267
Naltrexone-bupropion	4455	3977	3871	3404	2997	2690	2409

Error bars indicate 95% confidence intervals.

Table 5. Most Common Adverse Effects Leading to Discontinuation of Study Drug

Adverse Effects	Placebo, No. (%) (n = 4450)	Naltrexone-Bupropion, No. (%) (n = 4455)	*P* Value[a]
Any adverse effect	388 (8.7)	1253 (28.1)	<.001
Gastrointestinal	84 (1.9)	631 (14.2)	<.001
Nausea	21 (0.5)	333 (7.5)	<.001
Constipation	15 (0.3)	123 (2.8)	<.001
Vomiting	1 (<0.1)	87 (2.0)	<.001
Central nervous system	52 (1.2)	226 (5.1)	<.001
Tremor	0	77 (1.7)	<.001
Dizziness	7 (0.2)	62 (1.4)	<.001
Headache	14 (0.3)	51 (1.1)	<.001
Psychiatric disorders	39 (0.9)	136 (3.1)	<.001
Insomnia	16 (0.4)	35 (0.8)	.01
Anxiety	8 (0.2)	26 (0.6)	.002
Hallucinations	0	11 (0.2)	<.001
Depression	9 (0.2)	5 (0.1)	.28
Increased blood pressure	23 (0.5)	39 (0.9)	.04
Palpitations	5 (0.1)	19 (0.4)	.004
Feeling jittery	1 (<0.1)	15 (0.3)	<.001
Flushing or hot flashes	2 (<0.1)	13 (0.3)	.004
Fatigue	1 (<0.1)	12 (0.3)	.002

[a] By 2-sided χ^2 test.

The success of the 2-stage approach to drug development relies on the maintenance of strict confidentiality during the time from submission of the initial interim results until completion of the definitive safety study. In practice, a defined team from the trial sponsor is provided with the interim results and submits the drug for approval but has no ongoing involvement with the study. The company business leadership, the study's academic leadership, and all other study personnel remain blinded until the definitive study is completed. The FDA also agreed to maintain confidentiality for the 25% interim data until the trial was completed.

During our trial, publication of a patent submitted by Orexigen, along with a subsequent submission by the company to the Securities and Exchange Commission,[9] resulted in public release of the 25% interim results of the trial. The published patent claimed a method of reducing cardiovascular risk based on a 41% reduction in cardiovascular risk with naltrexone-bupropion, which were interpreted in the media as showing cardiovascular benefit. The study academic leadership subsequently recommended and the sponsors agreed to terminate the trial.

As a result of these events, interpretation of the results of the trial involves complex statistical issues. Noninferiority testing to rule out a doubling of cardiovascular risk (an upper 95% confidence limit of the HR not exceeding 2.0) was successfully completed after accrual of 94 (25%) of the planned 378 events (Table 4). Accordingly, it is possible to conclude that naltrexone-bupropion does not double cardiovascular risk based on the preplanned 25% interim analysis, but it is not possible to draw any conclusions related to the noninferiority margin of 1.4. A new cardiovascular outcome trial will be required to address the regulatory mandate to rule out a noninferiority margin of 1.4 but will not be available for a minimum of 3 to 4 years.

Per the study design, the data monitoring committee could consider stopping the trial for overwhelming evidence of efficacy or harm based on interim analyses at 50% and 75% of trial completion with statistical adjustments using O'Brien-Fleming boundaries. The study design did not allow early termination for demonstration of noninferiority. The primary outcome data reported in this manuscript were determined using the 50% interim analysis (192 events), the last preplanned analysis performed prior to termination of the trial. The HRs along with the 99.7% confidence intervals reflect the appropriate statistical adjustments for the 50% interim analysis. No *P* values for either superiority or noninferiority are reported because the results of the prematurely terminated trial cannot be used to rigorously address either superiority or the prespecified noninferiority margin of 1.4. An additional sensitivity analysis was performed using the final data available at the time of last patient contact and showed less favorable findings than the primary analysis. The final data include 243 primary composite end points, approximately 64% of the intended 378 events.

In clinical trials, an ITT analysis is preferred because it is the only analysis that preserves the integrity of randomization and represents a conservative approach to assessment of efficacy. However, in a safety study, particularly one with a low adherence rate, the on-treatment analysis can provide additional insight because it reflects outcomes in patients while they were actually taking the medication under study. In a safety study, when adherence rates are low, the ITT analysis can result in a false-positive declaration of noninferiority. Accordingly, an on-treatment analysis is essential to confirm findings derived from the ITT analysis.

In our trial, the on-treatment analysis shows HRs that are less favorable (higher) than the ITT analysis for naltrexone-bupropion. This finding is particularly evident for the 25%

interim analysis showing 24 more primary events for the placebo vs naltrexone-bupropion treatment group in the ITT analysis (59 vs 35) but only 7 excess events in the placebo group for the on-treatment analysis (30 vs 23) (Table 4). The most favorable component of the primary end point at the 25% interim analysis, cardiovascular death, 19 events for placebo vs 5 for naltrexone-bupropion, was driven almost exclusively by a 12-to-1 imbalance in death favoring naltrexone-bupropion among patients who were no longer taking study drug. These observations suggest that any inference regarding noninferiority must be viewed cautiously pending completion of an adequately powered new clinical trial, preferably with greater adherence to treatment.

The trial offers some useful findings with respect to the effectiveness of naltrexone-bupropion as a treatment for obesity and provides insights about the conduct of future trials of obesity treatments. For the ITT population, at trial completion, the observed weight loss with naltrexone-bupropion was modest, with a mean reduction of 3.9 kg (95% CI, −4.1 to −3.7 kg), 3.6% of initial body weight, compared with 1.2 kg (95% CI, −1.3 to −1.0 kg) in the placebo group (Figure 4). Compared with placebo, the incremental weight loss was approximately 2.7 kg (95% CI, −2.9 to −2.5 kg), or 2.5% of body weight. The modest weight loss efficacy was likely related to low adherence to treatment, with approximately 63% of naltrexone-bupropion patients and 74% of placebo patients no longer taking study drug after 12 months.

A relatively low adherence rate was anticipated in the design of the trial. Patients were discontinued from treatment at 16 weeks (but remained in the ITT population) if they lost less than 2% of initial body weight, an approach selected by the FDA, sponsor, and academic leadership to reflect the use of antiobesity agents in clinical practice. Patients and physicians do not persist with an obesity treatment in the absence of weight loss. Patients with obesity are often dispirited and easily frustrated by their inability to lose weight permanently after years of trying.[17,18] These experiences may contribute to suboptimal adherence to treatment recommendations and poor study retention. Despite maximal efforts, poor adherence and modest retention represent challenges to the conduct of such trials. Because cardiovascular outcomes trials typically require many patient-years of exposure, successfully completing such trials will require intensive efforts to promote adherence to study drugs and retention of patients in the trial. The low adherence rate and early termination of our trial does not allow any reliable conclusions about the long-term safety of naltrexone-bupropion.

Because blood pressure and heart rate increases represented the major reasons for concern about the cardiovascular safety of naltrexone-bupropion, we collected these vital sign measurements throughout the trial. Post hoc analysis of blood pressure and heart rate after 16 weeks of treatment, when adherence was still relatively high, showed a mean increase in blood pressure for naltrexone-bupropion compared with placebo averaging only 0.46 mm Hg (95% CI, 0.01-0.92 mm Hg) and mean increase in heart rate of 0.45/min (95% CI, 0.11/min to 0.78/min). These changes are similar to those observed during previous studies of naltrexone-bupropion. Adverse effects leading to study drug discontinuation were relatively common, occurring in 28.1% of naltrexone-bupropion–treated patients and 8.7% of placebo-treated patients ($P < .001$). The most common adverse effects were gastrointestinal and central nervous system symptoms (Table 4).

The events leading to the termination of the study serve as a valuable reminder of the importance of maintaining confidentiality during ongoing trials. Premature release of interim data can result in inappropriate prejudgment about the benefits or risks of the studied therapy and make completion of the trial highly problematic. An FDA guidance for industry explicitly states that interim data from an ongoing clinical trial should remain confidential and warns that "such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of analyses."[19] Prior to public release of the 25% interim data, the FDA had already appropriately concluded that the knowledge of the results by business interests within the sponsor constituted an unacceptable breach of confidentiality that precluded use of the trial to meet the postapproval regulatory requirement.[11]

The findings of this study illustrate the importance of confidentiality for early interim data. In this case, the 25% interim data (Table 4) showed a point estimate for the HR for the primary end point of 0.59, although with wide confidence intervals (95% CI, 0.39-0.90). However, after an additional 25% of data were collected, the HR increased to 0.88 (99.7% CI, 0.58-1.34). For the final end-of-study analysis, the HR increased further to 0.95 (99.7% CI, 0.65-1.38), such that any potential benefit suggested in the earlier analysis was no longer apparent.

Our study has both strengths and weaknesses. It represents one of the few cardiovascular outcomes trials of pharmacological agents used to treat obesity and, despite early termination, collected data on a large number of cardiovascular events. The unplanned early termination represents an important weakness that prevented the trial from achieving its full potential. The poor adherence rate was also a weakness but may represent the typical pattern observed with antiobesity pharmacological therapies in clinical practice. The observations derived from this study provide useful insights for other investigators designing future outcomes trials for other obesity treatments.

Conclusions

Among overweight or obese patients at increased cardiovascular risk, based on the interim analyses performed after 25% and 50% of planned events, the upper limit of the 95% confidence interval of the HR for MACE for naltrexone-bupropion treatment, compared with placebo, did not exceed 2.0. However, because of the unanticipated early termination of the trial, it is not possible to assess noninferiority for the prespecified upper limit of 1.4. Accordingly, the cardiovascular safety of this treatment remains uncertain and will require evaluation in a new adequately powered outcome trial.

ARTICLE INFORMATION

Author Contributions: Dr Nissen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Nissen, Wadden, Buse, Bakris, Smith.
Acquisition, analysis, or interpretation of data: Nissen, Wolski, Prcela, Buse, Perez, Smith.
Drafting of the manuscript: Nissen, Wolski, Prcela, Bakris, Perez.
Critical revision of the manuscript for important intellectual content: Nissen, Wadden, Buse, Bakris, Perez, Smith.
Statistical analysis: Nissen, Wolski.
Obtained funding: Nissen, Perez.
Administrative, technical, or material support: Nissen, Prcela, Bakris, Perez.
Study supervision: Nissen, Wadden, Buse, Perez, Smith.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Nissen reports grants from the Medicines Company, Amgen, Pfizer, AstraZeneca, Esperion Therapeutics, Eli Lilly, and Cerenis. He consults with many pharmaceutical companies but requires any honoraria or consulting fees be paid directly to charity so that he receives neither income nor a tax deduction. Dr Wadden reports receipt of personal fees for serving on the executive steering committee for the current study. Dr Buse reports fees for consultation to the University of North Carolina under contract and travel/meals/lodging for contracted activities from a variety of companies; grants from GlaxoSmithKline, Astellas, MacroGenics, and Intarcia Therapeutics; and membership on a variety of nonprofit boards (eg, American Diabetes Association, DiabetesSisters, Taking Control of Your Diabetes, AstraZeneca Healthcare Foundation, Bristol-Myers Squibb Together on Diabetes Foundation, the National Diabetes Education Program). Dr Bakris reports consultancy for AbbVie, Takeda, Medtronic, Relypsa, Boehringer-Ingelheim, Janssen, AstraZeneca, Bayer, and Merck. Dr Perez was previously an employee of Takeda. Dr Smith reports grants/personal fees from Takeda. No other disclosures were reported.

Funding/Support: The study was sponsored by Orexigen Therapeutics Inc, La Jolla, California, and Takeda Pharmaceuticals International, Deerfield, Illinois.

Role of the Funders/Sponsor: The sponsors were involved in the design and conduct of the study and collection and management of the data. Both the Cleveland Clinic Center for Clinical Research and the sponsors had access to the full trial database for analysis. The sponsors had the right to comment on the manuscript, but final decisions on content rested with the academic authors.

Group Information: *Executive steering committee:* Steven S. Nissen, MD (executive steering committee chairman and study co–principal investigator), Cleveland Clinic, Department of Cardiovascular Medicine, Cleveland, Ohio, George L. Bakris, MD, University of Chicago Medicine, director, ASH Comprehensive Hypertension Center, Chicago, IL, John B. Buse, MD, PhD, University of North Carolina School of Medicine, Chapel Hill, NC; Thomas A. Wadden, PhD, University of Pennsylvania Perelman School of Medicine, Center for Weight and Eating Disorders Department of Psychiatry, Philadelphia, PA, Steven R. Smith, MD, Translational Research Institute for Metabolism and Diabetes, Florida Hospital, Sanford-Burnham Medical Research Institute, Orlando, FL. *Data monitoring committee:* Thomas R. Fleming (data monitoring committee chair and biostatistician); Paul W. Armstrong; Darren K. McGuire; Domenica M. Rubino; Ihsan M. Salloum; Arya M. Sharma. *Independent statistical center supporting the data monitoring committee:* Axio Research, Seattle, WA. *Academic research organization:* C5Research–Cleveland Clinic Coordinating Center for Clinical Research (Cleveland, OH): A. Michael Lincoff, MD (director), Lisa Prcela, Dianna Bash, Elizabeth Fabry, Denise Mason, Mingyan Shao, Michelle Strzelecki, Kathy E. Wolski. *Contract research organization:* PRA Health Sciences (Blue Bell, PA): Maria C. Harrison (vice president), Dana McCarthy, Kathryn Cheatle, Chris Meussner, Erica Rohrbach, Matt Zimmerman. *Clinical events committee:* C5Research–Cleveland Clinic Coordinating Center for Clinical Research (Cleveland, OH): Michael Faulx, MD (clinical events committee chairperson), Venu Menon, MD (clinical events committee director), Mary Jo Heckman RN, Michael Chenier, MD, Paul Cremer, MD, Irene Katzan, MD, Jason Lappe, MD, David Newton, MD, Lee Pierson, MD, Andrew Russman, MD, Daniel Sedehi, MD, Jitendra Sharma, MD, Ken Uchino, MD. *Takeda Pharmaceuticals International* (Deerfield, IL): Study leadership: Penny Fleck, Stuart Kupfer, MD, Orlando Bueno, MD, Jay Liu, Kraig Keeter, Jason Gans, Diane Balma, Ming Jing, John Marcinak, MD, Cong Han, Hung Lam, Yinzhong Chen, Nina Barcha, Alison Handley. *Orexigen Therapeutics Inc* (La Jolla, CA): Study leadership: Toni Foster, Amy Halseth, Dan Cooper, Daun Bahr, Kevin Shan, Dawn Viveash, Kristin Taylor, Ann Ashinger, Colleen Burns. *Light Investigators (Number of Enrolled Patients):* Laura Akright, NECRSA, LLC, Schertz, TX (142); Kevin D. Cannon, PMG Research of Wilmington LLC, Wilmington, NC (136); Douglas R. Schumacher, Radiant Research Inc, Columbus, OH (119); Lars H. Runquist, PMG Research of Charleston, Mount Pleasant, SC (112); William P. Jennings, Radiant Research Inc, San Antonio, TX (112); Harry I. Geisberg, Radiant Research Inc, Anderson, SC (112); Margaret Rhee and Hassan Malik, Radiant Research Inc, Akron, OH (110); Larry Kotek and Tami Helmer, Radiant Research Inc, Edina, MN (109); Leslie Tharenos, Radiant Research Inc., St Louis, MO (106); Adnan A. Aslam, Northwest Houston Heart Center, Tomball, TX (104); John Rubino, PMG Research of Raleigh, Raleigh, NC (104); Muna Abuerreish and Mary Cotharp, Radiant Research, Overland Park, KS (103); Michael R. Adams, Radiant Research Inc, Murray, UT (100); Michele D. Reynolds, Radiant Research Inc, Dallas, TX (100); William T. Ellison, Radiant Research, Greer, Greer, SC (95); George L. Raad, PMG Research of Charlotte, Charlotte, NC (94); Michael Glenn Winnie, Corpus Christi Family Wellness Center, Corpus Christi, TX (94); Jonathan Paul Wilson, PMG Research of Winston Salem, Winston Salem, NC (92); Linda Murray, Radiant Research Inc, Pinellas Park, FL (91); Robert E. McNeill, PMG Research of Salisbury, LLC, Salisbury, NC (86); Martin L. Throne, Radiant Research Inc., Atlanta, GA (83); Debra L. Weinstein, ZASA Clinical Research, Boynton, FL (79); Bernard P. Grunstra, PMG Research of Bristol, Bristol, TN (79); Pink L. Folmar Jr and Gordon T. Conner, Radiant Research/Simon Williamson Clinic, Birmingham, AL (79); Phyllis D. Marx and Kent Kamradt, Radiant Research Inc, Chicago, IL (76); William J. Randall, PriMed Clinical Research, Kettering, OH (74); Stephen L. Aronoff, Research Institute of Dallas, Dallas, TX (68); Opada Alzohaili, Alzohaili Medical Consultants, Dearborn, MI (67); Randall J. Severance, Radiant Research Inc, Chandler, AZ (67); David L. Bolshoun, Clinical Research Advantage Inc/Clinic Health Services of Colorado Inc, Centennial, CO (66); Leslie Cho, The Cleveland Clinic Foundation, Cleveland, OH (66); Kelli K. Maw and James L. Andersen, Meridien Research, Brooksville, FL (65); Wayne L. Harper, Wake Research Associates LLC, Raleigh, NC (64); John K. Earl, PMG Research of Hickory, LLC, Hickory, NC (64); Jean Foucauld, Cardiology Partners Clinical Research Institute, Wellington, FL (63); Hubert Reyes, MediSphere Medical Research Center LLC, Evansville, IN (63); Michael J. Noss, Radiant Research, LLC, Cincinnati, OH (59); Frank H. Morris, Lutherville Personal Physicians, Lutherville, MD (58); Terry L. Poling, Heartland Research Associates LLC, Wichita, KS (57); Steven K. Sooudi, DiscoveResearch Inc, Beaumont, TX (57); Dennis J. Levinson, Chicago Clinical Research Institute Inc, Chicago, IL (56); James Blankenship and Peter B. Berger, Geisinger Clinic/Geisinger Medical Center, Danville, PA (53); Vicki S. Blumberg, Stamford Therapeutics Consortium, Stamford, CT (53); Elie Hage-Korbin, Kore Cardiovascular Research, Jackson, TN (53); M. Shakil Aslam, Beacon Medical Group Clinical Research, South Bend, IN (52); S. Keith Smith, Burke Primary Care, Morganton, NC (52); Carl P. Griffin, Lynn Health Science Institute, Oklahoma City, OK (52); Timothy M. Koehler, Heartland Research Associates LLC, Wichita, KS (52); Bruce T. Bowling, Regional Clinical Research Inc, Endwell, NY (52); Michael R. McGuire, Lovelace Scientific Resources Inc, Albuquerque, NM (51); Barry D. Bertolet, Cardiology Associates Research LLC, Tupelo, MS (50); Stephen M. Minton, Alexandria Clinical Research LLC, Alexandria, VA (50); Alan J. Kivitz, Altoona Center for Clinical Research, Duncansville, PA (50); Bruce G. Rankin, Avail Clinical Research, LLC, Deland, FL (50); Ranjan P. Shah, Clinical Trial Network, Houston, TX (50); Martin Van Cleeff, PMG Research of Raleigh, LLC d/b/a PMG Research of Cary, Cary, NC (49); Otis Barnum, KAMP Medical Research Inc., Natchitoches, LA (49); Anuj Bhargava, Iowa Diabetes and Endocrinology Research Center, Des Moines, Iowa (48); David J. Butuk, Solaris Clinical Research, Meridian, ID (47); Steven Smith, Translational Research Institute for Metabolism and Diabetes, Orlando, FL (47); Harry Earl Studdard, Coastal Clincal Research Inc, Mobile, AL (46); Cynthia Becher Strout, Coastal Carolina Research Center, Mount Pleasant, SC (46); Chander M. Arora, RAS Health LTD, Marion, OH (45); Lawrence W. Whitlock, Southwind Medical Specialists, Memphis, TN (45); Harvey Resnick, R/D Clinical Research Inc, Lake Jackson, TX (45); Muhammad A. Khan, North Dallas Research Associates, McKinney, TX (45); Max A. Nevarez, Clinical Research Advantage Inc/ Colorado Springs Health Partners, PC, Colorado Springs, CO (45); Paul H. Wakefield, PMG Research of Knoxville, Knoxville, TN (45); Stephen W. Halpern, Radiant Research Inc, Santa Rosa, CA (45); Ernie Riffer, Clinical Research Advantage Inc/Central

Phoenix Medical Clinic, LLC, Phoenix, AZ (44); Nathan Segall, Clinical Research Atlanta, Stockbridge, GA (44); Harold E. Bays, L-MARC Research Center, Louisville, KY (43); Joseph L. Lillo, Elite Clinical Studies LLC, Phoenix, AZ (43); Albert Q. Tejada, Radiant Research Inc., Scottsdale, AZ (43); Eli M. Roth and Matthew D. Wenker, Sterling Research Group, Ltd, Cincinnati, OH (42); Steven A. Geller, Centennial Medical Group, Elkridge, MD (41); Ronald I. Harris, Geisinger Specialty Clinic, Wilkes Barre, PA (41); Jon O. Ebbert, Mayo Clinic, Rochester, MN (41); Seth H. Baker, Indian River Medical Associates–Cardiology, Vero Beach, FL (41); Warren Shu and Gary L. Sutter, HealthCare Partners Medical Group, Pasadena, CA (40); Holly Dushkin, Alan E. Kravitz, Nancy J. Tresser and Alan C. Wine, Rapid Medical Research Inc, Cleveland, OH (40); Robert J. Buynak, Buynak Clinical Research, Valparaiso, IN (39); David R. Allen, Clinical Research Advantage Inc/Internal Medicine Physicians, Omaha, NE (39); Peter Rives and Gary Elkin, Southeast Regional Research Group, Savannah, GA (39); Rajesh J. Patel, Lycoming Internal Medicine Inc, Jersey Shore, PA (38); Paul D. Rosenblit, Diabetes/Lipid Management and Research Center, Huntington Beach, CA (38); William L. Abraham, Radiant Research Inc, Tucson, AZ (38); Robert A. Strzinek, Protenium Clinical Research, LLC, Hurst, TX (37); Timothy R. Smith, Mercy Health Research, Saint Louis, MO (37); Sanford N. Plevin, Suncoast Clinical Research Inc, New Port Richey, FL (36); Robinson Koilpillai and Richard Giusti, Clinical Research of Central Florida, Winter Haven, FL (36); Mark Heiman, Cardiology Associates of Fairfield County, PC, Stamford, CT (36); Adeniyi O. Odugbesan, Physicians Research Associates LLC, Lawrenceville, GA (36); Isaac Dor, Clinical Investigations Specialists Inc, Gurnee, IL (36); Zulfiquar Bhatti, Columbus Regional Research Institute, Columbus, GA (36); William R. Felten, MidMichigan Medical Center Midland, Midland, MI (35); Brenda C. Peart, Southwest Heart Group, Tucson, AZ (34); Rao V. C. Gudipati, Michigan Cardiovascular Institute, Saginaw, MI (33); Mark A. Stich, Westside Center for Clinical Research, Jacksonville, FL (33); Damodhar P. Suresh, Saint Elizabeth Healthcare, Crestview Hills, KY (33); Michael R. Seidner and Jack C. Rosenfeld, Green and Seidner Family Practice Associates, Lansdale, PA (33); Samer Nakhle, Palm Research Center, Las Vegas, NV (32); Barry C. Lubin, National Clinical Research-Norfolk Inc, Norfolk, VA (32); Alfred N. Poindexter III, Advances In Health Inc, Houston, TX (32); Donald P. Hurley, Medical Research South LLC, Charleston, SC (32); E. Clark Cullen, Sunstone Medical Research LLC, Medford, OR (32); Mark A. Turner, Advanced Clinical Research, Meridian, ID (32); Gerald R. Shockey, Clinical Research Advantage Inc./Desert Clinical Reseach, LLC, Mesa, AZ (32); Roddy P. Canosa Frank W. Corbally, Northern Lancaster County Medical Group affiliate of Wellspan Health Medical Group, Ephrata, PA (32); Lisa M. Cohen, Suncoast Clinical Research Inc, New Port Richey, FL (32); Sabrina A. Benjamin, Universal Research Group, Tacoma, WA (32); David Fitz-Patrick, East-West Medical Research Institute, Honolulu, HI (32); Kenneth M. Maynard, Investigator's Research Group, LLC, Brownsburg, IN (31); Robert J. Weiss, Maine Research Associates, Auburn, ME (31); Dale C. Allison, Hillcrest Family Health Center, Waco, TX (31); Douglas Young, Northern California Research, Sacramento, CA (31); Ralph David Wade, Wade Family Medicine Inc, Bountiful, UT (30); Raymond E. Jackson, QUEST Research Institute, Bingham Farms, MI (30); Miguel E. Trevino, Innovative Research of West Florida Inc, Clearwater, FL (29); Murray A. Kimmel, Accelovance, Melbourne, FL (29); Matthew D. Acampora, The Center For Nutrition and Preventive Medicine, Charlotte, NC (29); Gigi C. Lefebvre, Meridien Research, St Petersburg, FL (29); Louis M. Stephens Jr, Palmetto Clinical Trials Services LLC, Fountain Inn, SC (28); Jennifer S. Kay, Clinical Research Advantage Inc/ Ridge Family Practice, Council Bluffs, IA (28); Kenneth Cohen, New West Physicians, PC, Golden, CO (27); Jay C. Anderson, Internal Medical Associates of Grand Island PC, Grand Island, NE (27); Robert Lipetz, Encompass Clinical Research, Spring Valley, CA (27); Bindu Lal and Armen H. Arslanian, Beacon Clinical Research, LLC, Brockton, MA (27); Bhola Rama, Rama Research, LLC, Marion, OH (27); Ravi S. Bhagwat, Cardiovascular Research of Northwest Indiana LLC, Munster, IN (27); Jack D. Wahlen, Advanced Research Institute, Ogden, UT (26); Jeffrey G. Shanes, Consultants in Cardiovascular Medicine, Melrose Park, IL (26); Michelle Welch, Cosano Clinical Research, San Antonio, TX (26); Ronald Blonder, UCH-MHS, Colorado Springs, CO (26); Michael Jacobs, Clinical Research Consortium, Las Vegas, NV (25); Irving K. Loh, Westlake Medical Research, Thousand Oaks, CA (25); William Saway, Columbia Medical Practice, Columbia, MD (25); David Radin, Stamford Therapeutics Consortium, Stamford, CT (25); Anthony Alfieri, Alfieri Cardiology, Newark, DE (25); Judith L. Kirstein, Advanced Clinical Research, West Jordan, UT (25); William Gonte, American Center for Clinical Trials, Southfield, MI (24); Jeffrey Rothman, University Physicians Group Research Division, Staten Island, NY (24); O. Michael Obiekwe, Atlanta Ropheka Medical Center/APSMO, Riverdale, GA (24); Donna M. DeSantis, Clinical Research Advantage Inc/ East Valley Family Physicians, PLC, Chandler, AZ (23); Robert Lamar Parker, Lyndhurst Clinical Research, Omaha, NE (23); Eric M. Ball, Walla Walla Clinic, Walla Walla, WA (23); Caroline M. Apovian, Boston University Medical Center, Boston, MA (23); Rene Casanova, SouthEast Medical Centre, Oakland Park, FL (23); Cezar Staniloae, Gotham Cardiovascular Research, PC, New York, NY (23); John J. Champlin, Med Center, Carmichael, CA (23); Kari T. Uusinarkaus, Clinical Research Advantage Inc/ Colorado Springs Health Partners, PC, Colorado Springs, CO (22); Daniel Weiss, Your Diabetes Endocrine Nutrition Group Inc, Mentor, OH (22); Anthony J. Bartkowiak Jr, Blair Medical Associates, Inc, Altoona, PA (22); Paul C. Norwood, Valley Research, Fresno, CA (22); David M. Barker, Chattanooga Medical Research LLC, Chattanooga, TN (22); John Buse, UNC Diabetes Care Center, Chapel Hill, NC (22); Daniel F. Sousa, Genesis Clinical Research and Consulting LLC, Fall River, MA (22); Andrea L. Phillips, Phillips Medical Services PLLC, Jackson, MS (22); Dean J. Kereiakes, The Carl and Edyth Lindner Center for Research and Education at The Christ Hospital, Cincinnati, OH (22); John Agaiby, Clinical Investigation Specialists Inc, Kenosha, WI (22); Scott Sulman, Geisinger Clinic/Geisinger Medical Group-Scenery Park, State College, PA (22); Mark L. Warren, Physician's East PA Endocrinology, Greenville, NC (21); John Hoekstra and John K. Scott, National Clinical Research-Richmond Inc, Richmond, VA (21); Oliver T. Willard and William E. Fowler, Advanced Research Associates–Self Medical Group, Hodges, SC (20); Thomas A. McKnight, Clinical Research Advantage Inc/Prairie Fields Family Medicine, PC, Fremont, NE (20); Patrick O'Neil, MUSC Weight Management Center, Charleston, SC (20); Harry Collins, Anderson and Collins Clinical Research Inc, Edison, NJ (20); Randall T. Huling Jr, Olive Branch Family Medical Center, Olive Branch, MS (19); Judith L. White, Holston Medical Group, Kingsport, TN (19); Keith D. Klatt, Columbia Research Group Inc, Portland, OR (19); Mandeep S. Oberoi, Central Jersey Medical Research Center, Elizabeth, NJ (19); Samuel O. Teniola, Samuel O. Teniola Private Practice/APSMO, Atlanta, GA (19); Robert G. Ashley Jr, Florida Research Network, Gainesville, FL (19); Kurt Lesh and William Tyler Stone, Lynn Institute of the Rockies, Colorado Springs, CO (19); Harold K. Cathcart, Northside Internal Medicine, Spokane, WA (18); Michael Castro, HOPE Research Institute, Peoria, AZ (18); Steven Hearne, Delmarva Heart and Research Foundation Inc, Salisbury, MD (18); Alan H. Wiseman, Eastern Maine Medical Center/ Northeast Cardiology, Bangor, MA (18); Krishna Kumar Pudi, Upstate Pharmaceutical Research, Greenville, SC (18); Frank A. McGrew III, Stern Cardiovascular Foundation Inc, Germantown, TN (17); William R. Palmer, Westroads Clinical Research Inc, Winston-Salem, NC (17); Clifford J. Molin, Clinical Research Advantage Inc, Las Vegas, NV (17); Barry K. McLean, Central Alabama Research, Birmingham, AL (16); Robin Kroll, Seattle Women's Health Research Gynecology, Seattle, WA (16); Peter J. Winkle, Anaheim Clinical Trials LLC, Anaheim, CA (16); Jasjit S. Walia, NJ Heart, Linden, NJ (16); Uma Rangaraj, Arthritis and Diabetes Clinic Inc, Monroe, LA (16); Stuart J. Simon, Georgia Clinical Research, Austell, GA (16); Philip S. Behn, Premier Healthcare LLC, Bloomington, IN (16); Kenneth A. Morris, Bensalem Medical Practice, Bensalem, PA (15); Peter Rees, ActivMed Practices and Research Inc, Methuen, MA (15); Steven Zeig, Pines Clinical Research Inc, Pembroke Pines, FL (15); Philip A. Levin and James H. Mersey, MODEL Clinical Research, Baltimore, MD (15); Eric Lo, Edgewater Medical Research Inc, New Smyrna Beach, FL (15); Timothy D. Wingo and Eugene F. Schwarz, Ellipsis Research Group LLC, Columbia, SC (15); Gary E. Ruoff, Westside Family Medical Center PC, Kalamazoo, MI (15); Robert A. Cohen, Cohen Medical Associates, PA, Delray Beach, FL (14); Clancy Cone, Montana Medical Research Inc, Missoula, MT (14); Kenneth Hershon, North Shore Diabetes and Endocrine Associates, New Hyde Park, NY (14); Kenneth Blaze, South Broward Research, LLC, Pembroke Pines, FL (14); William Graettinger, Reno Clinical Trials, Sparks, NV (14); William D. Doty, Cardiology Consultants, Pensacola, FL (14); Philip O'Donnell, Selma Medical Associates, Winchester, VA (14); Marina Raikhel, Torrance Clinical Research Institute Inc, Lomita, CA (14); Walter S. Patton, Quality of Life Medical & Research Center LLC, Tucson, AZ (13); Mohammad Riaz, Bayview Research Group LLC, Paramount, CA (12); Michael W. Warren, Research Across America, Reading, PA (12); Troy A. Thompson, Southwestern Medical Clinic Lakeland HealthCare Affiliate, Stevensville, MI (12); Ronald K. Mayfield, Mountain View Clinical Research Inc, Greer, SC (12); Bruce A. Barker, Delaware Research Group LLC, Delaware, OH (16); William Randolph Wainwright, Baptist Heart Specialists, Jacksonville, FL (11); Rita B. Chuang and Aaron Adaoag, Clinical Research Advantage Inc/Rita B. Chuang, MD, Henderson, NV (11); Michael G. Del Core, CHI Health Alegent

Creighton Clinic Cardiology, Omaha, NE (11); Veita J. Bland, Bland Clinic PA, Greensboro, NC (10); John B. Buse, UNC Diabetes Research at Eagle Physicians, Greensboro, NC (10); Matthew J. Budoff, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA (10); Ken Fujioka, Scripps Clinical Research Services, La Jolla, CA (10); David B. Jack, Lone Peak Family Medicine, Draper, UT (10); Thomas L. Davis III, Integrated Research Group Inc, Riverside, CA (10); Michael J. Guice, American Institute of Research, Los Angeles, CA (10); Mark E. Kutner, Suncoast Research Group LLC, Miami, FL (10); Brian D. Snoddy, Birmingham Heart Clinic PC, Birmingham, AL (10); John Pullman, Mercury Street Medical Group, PLLC, Butte, MT (9); Imran Dotani and Steven R. Wanzek, McFarland Clinic, Ames, IA (9); Mukarram A. Baig, Heart Care Center of NW Houston, Houston, TX (9); Jung Oh and Richard B. Stewart, Perimeter Institute for Clinical Research Inc DBA: PICR Clinic, Atlanta, GA (9); Sunil Bhoyrul, XiMED Center for Weight Management, La Jolla, CA (8); Glenn R. Davis and Larry S. Watkins, Drs. Glenn Davis and Dennis Dean Kumpuris, PA, Little Rock, AR (8); Lindsey White, Eastern Carolina Cardiovascular, Elizabeth City, NC (8); Timothy Bailey, AMCR Institute Inc, Escondido, CA (8); Frank Greenway, Pennington Biomedical Research Center, Baton Rouge, LA (8); Thomas M. Wade, South Florida Research Advantage LLC, Pembroke Pines, FL (8); Neville Bittar, Gemini Scientific LLC, Madison, WI (8); Reza Banifatemi and John C. Corbelli, Buffalo Cardiology and Pulmonary Associates, Williamsville, NY (7); Paul R. Hermany, Grand View–Lehigh Valley Health Services, Buxmont Cardiology Division, Sellersville, PA (7); Danny Sugimoto, Cedar-Crosse Research Center, Chicago, IL (7); Samuel Klein, Washington University School of Medicine, St. Louis, MO (7); Samuel Joseph Tarwater, Digestive Health Specialists of the Southeast DBA Tarheel Clinical Research, LLC, Dothan, AL (7); John J. Hunter, Santa Rosa Cardiology Medical Group, Santa Rosa, CA (7); Philip Pearlstein, Pearl Clinical Research Inc, Norristown, PA (7); Paramjit Parmar and Russel W. Simpson, Lynn Institute of Denver, Denver, CO (7); Jaime David Sandoval, Padre Coast Medical Research, Corpus Christi, TX (7); Larkin Wadsworth III, Sundance Clinical Research LLC, St. Louis, MO (7); Tiffany M. Pluto, Fay West Family Practice, Scottdale, PA (7); Stephen H. Fehnel, Reading Health Physician Network–Women's Clinic and IVF–Fertility, West Reading, PA (6); Robert J. Helm, Investigative Clinical Research of Indiana LLC, Elwood, IN (6); Nampalli K. Vijay, Aurora Denver Cardiology Associates, PC, Denver, CO (6); Richard L. Beasley, Health Concepts, Rapid City, SD (5); Priscilla L. Hollander, Baylor Endocrine Center, Dallas, TX (5); Naseem A. Jaffrani, Alexandria Cardiology Clinic, Alexandria, LA (5); John V. Bernard, Wellness and Research Center, Belvidere, NJ (5); Senthil N. Sundaram, PMG Research of Raleigh, Raleigh, NC (4); Jeffrey P. Barasch, Better Breathing, Ridgewood, NJ (4); Dan A. Streja, Infosphere Clinical Research Inc, West Hills, CA (4); Eric D. Blakney, Premier Internal Medicine, Memphis, TN (4); Archie Hearne, Preferred Research Partners Inc, Little Rock, AR (3); Bruce Rashbaum, Capital Medical Associates, PC, Washington, DC (3); John P. Foreyt, Baylor College of Medicine, Houston, TX (3); Hani Kozman, SUNY Upstate Medical University, Syracuse, NY (2); Paul McLaughlin, Paul McLaughlin, MD, Private Practice, Mount Sterling, KY (2); Patricia Bearnson, Office of Patricia Bearnson, MD, Salt Lake City, UT (1); Sherry Megalla and Narendra Bhalodkar, Bronx Lebanon Hospital Center, Bronx, NY (1); Pratibha Vemulapalli, Medical Arts Pavilion, Bronx, NY (1).

Additional Contributions: Kye Gilder, PhD, and Preston Klassen, MD, Orexigen Therapeutics, were instrumental in designing and conducting the trial, participated in reviewing the manuscript, and made important contributions to the content. They did not receive financial compensation outside of their ususal salaries.

REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA*. 2012;307(5):491-497.

2. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA*. 2015;314(10):1021-1029.

3. Wing RR, Bolin P, Brancati FL, et al; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145-154.

4. James WP, Caterson ID, Coutinho W, et al; SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363(10):905-917.

5. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337(9):581-588.

6. Greenway FL, Fujioka K, Plodkowski RA, et al; COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595-605.

7. Wood S. FDA declines approval for Contrave diet drug; asks for CVD outcomes studies. February 1, 2011. http://www.medscape.com/viewarticle/736616. Accessed February 11, 2016.

8. Orexigen Therapeutics Inc. Orexigen and FDA identify a clear and feasible path to approval for Contrave: interim results from outcomes trial would support resubmission of Contrave NDA. http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle&ID=1608571. Accessed February 11, 2016.

9. US Securities and Exchange Commission. Form 8K [filed by Orexigen Therapeutics Inc]. March 3, 2015. https://www.sec.gov/Archives/edgar/data/1382911/000119312515074251/d882841d8k.htm. Accessed February 10, 2016.

10. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35(3):549-556.

11. Center for Drug Evaluation and Research, US Food and Drug Administration. Summary review of application number 200063Orig1s000. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200063Orig1s000SumR.pdf. Accessed February 10, 2016.

12. Feuerstein A. Orexigen weight-loss pill shows surprise heart-safety benefit. March 3, 2015. http://www.thestreet.com/story/13065624/1/orexigen-weight-loss-pill-shows-surprise-heart-safety-benefit.html. Accessed February 10, 2016.

13. O'Riordan M. LIGHT stopped: Contrave CVD safety study halted following premature release of data. May 12, 2015. http://www.medscape.com/viewarticle/844575. Accessed February 11, 2016.

14. Gadde KM, Parker CB, Maner LG, et al. Bupropion for weight loss: an investigation of efficacy and tolerability in overweight and obese women. *Obes Res*. 2001;9(9):544-551.

15. Greenway FL, Whitehouse MJ, Guttadauria M, et al. Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring)*. 2009;17(1):30-39.

16. US Food and Drug Administration. *Guidance for Industry: Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. December 2008. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed February 10, 2016.

17. Somerville R, McKenzie K, Eslami S, Breen C, O'Shea D, Wall P. Poor mental health in severely obese patients is not explained by the presence of comorbidities. *Clin Obes*. 2015;5(1):12-21.

18. Wadden TA, Bartlett S, Letizia KA, Foster GD, Stunkard AJ, Conill A. Relationship of dieting history to resting metabolic rate, body composition, eating behavior, and subsequent weight loss. *Am J Clin Nutr*. 1992;56(1)(suppl):203S-208S.

19. US Food and Drug Administration. *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees*. March 2006. http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf. Accessed February 10, 2016.