VI-0521 (QNEXA®) ADVISORY COMMITTEE BRIEFING DOCUMENT

NDA 022580

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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VIVUS, Inc.
1172 Castro Street
Mountain View, CA 94040
USA

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EXECUTIVE SUMMARY

QNEXA is an orally administered, once-daily weight loss therapy that contains a combination of immediate-release phentermine hydrochloride (PHEN) and extended-release topiramate (TPM). These two agents suppress appetite through complementary and distinct mechanisms (decreased hunger and increased satiety), leading to additive effects on weight loss. Both PHEN and TPM are U.S.-marketed drugs approved at higher doses than those contained in QNEXA.

VIVUS is seeking approval of QNEXA® (phentermine/topiramate) Extended-Release Capsules, for the treatment of adult obesity, including weight loss and maintenance of weight loss when used in conjunction with diet and exercise. If approved, QNEXA would be recommended for obese patients (body mass index [BMI] $\geq$30 kg/m^2) or overweight patients (BMI $\geq$27 kg/m^2) with obesity-related comorbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

Regulatory History

The original New Drug Application (NDA) for QNEXA was submitted to the Food and Drug Administration (FDA) on December 28, 2009 and was reviewed at a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on July 15, 2010. The NDA included results of a comprehensive clinical development program conducted by VIVUS specific to the efficacy and safety of three doses of QNEXA for the treatment of obesity. Because the active components, phentermine hydrochloride and topiramate, are FDA-approved products for other conditions at doses higher than those proposed in QNEXA, the NDA also relied in part on the FDA's previous determination of safety for these products.

FDA cited no deficiencies pertaining to the establishment of QNEXA efficacy in the NDA. FDA did, however, issue a Complete Response Letter (CRL) for QNEXA on October 28, 2010 based on two safety concerns related to the approved component products. First, the CRL requested a comprehensive assessment of topiramate's and phentermine/topiramate's teratogenic potential including a detailed plan and strategy to evaluate and mitigate any potential teratogenic risks in women of childbearing potential (WOCBP). Second, the CRL requested evidence that QNEXA-associated elevations in heart rate (mean 1.6 bpm on the Top dose) do not increase the risk for major adverse cardiovascular events, and the long term results from study OB-305, a recently-completed 52-week extension study conducted in a subset of patients who had completed study OB-303, one of the 1-year pivotal trials.

This Advisory Committee background material will review the overall efficacy and safety data for QNEXA, followed by a focused discussion on the CRL topics including potential risks associated with small elevations in heart rate and a review of clinical teratogenicity information.

With FDA's agreement, VIVUS resubmitted the NDA on October 17, 2011 with a contraindication for use of QNEXA in WOCBP. After further discussion with the agency, FDA has asked and VIVUS agreed to remove the contraindication for WOCBP because a contraindication typically indicates that a drug should not be used in that population because

of the risk of use clearly outweighs any possible therapeutic benefit. In addition, FDA asked that VIVUS include less restrictive elements in its REMS program that focus on patient and physician educational measures because it was concerned that more restrictive measures may result in greater off-label use of currently marketed topiramate and phentermine products to treat obesity in WOCBP without the benefit of an appropriate risk mitigation program. In response to these concerns, VIVUS removed the contraindication in WOCBP and modified its risk mitigation strategy.

FDA informed VIVUS that the revised contraindication should be for women who are pregnant, and that the contraindication need to state that if a woman becomes pregnant while taking QNEXA, treatment should be discontinued immediately.

QNEXA

QNEXA is an investigational weight-loss therapy that is a novel combination of low dose immediate-release phentermine (1/8 to 1/2 of currently approved dose) and extended-release topiramate (1/16 to 1/4 of currently approved dose); both drugs are approved and marketed in the United States. The prescription use of these drugs spans more than 52 years for phentermine and more than 15 years for topiramate. Phentermine hydrochloride, at a labeled dose up to 37.5 mg/day (Adipex-P® package insert 2005; **Appendix 10)**, is the most prescribed weight-loss drug in the U.S. with approximately 6.5 million prescriptions written in 2011 (Information Management System [IMS] data). A more recently approved formulation of phentermine, Suprenza™, was approved in 2011 (Suprenza™ package insert 2011; **Appendix 11**). The phentermine label, restricted to short-term management of obesity, limits its clinical application for the chronic treatment of obesity and weight-related comorbidities. The primary mechanism of action of phentermine for weight loss is an anorectic effect occurring through the release of norepinephrine in the hypothalamus.

Topiramate is approved for treatment of seizure disorders at recommended doses up to 400 mg/day and for migraine headache prophylaxis at recommended doses up to 100 mg/day (Topamax® package insert 2011; **Appendix 12**). More than 10 million prescriptions were written in 2011 for topiramate (IMS data). The majority of current topiramate use is in migraine prophylaxis. Available pharmacological evidence suggests that topiramate-induced weight loss may result from increased satiety due to decreased gastrointestinal motility (Topamax Summary Basis for Approval 1995), increased taste aversion (Supuran 2008), increased energy expenditure, and decreased caloric intake (Bray 2003; Richard 2000; Richard 2002; Picard 2000). Published clinical studies have shown that topiramate monotherapy produces significant and dose-related weight loss in conjunction with clinically meaningful improvements in lipids, glycemic control, and blood pressure (Ben-Menachem 2003; Wilding 2004; Bray 2003), which may, in part, be independent of weight loss (Stenlöf 2007; Astrup 2004). Topiramate, however, is associated with dose-limiting side effects which prevent or limit its use as a single agent at the doses necessary to produce significant weight loss or cardiometabolic benefits.

The efficacy and tolerability of QNEXA is based on complementary, multi-targeted pharmacology that provides significantly greater weight loss, at lower doses, than has been previously demonstrated for the respective components at any dose level. The ability to use

lower doses in combination that can achieve greater weight loss compared with the individual components is paramount to the positive risk/benefit relationship of QNEXA.

Medical Need

Results from the National Health and Nutrition Examination Survey, 2007-2008, indicate that approximately 68% of adults in the United States are obese or overweight (Flegal 2010). Obesity is associated with numerous comorbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, cancer, and type 2 diabetes (Must 1999; Poirier 2006). Epidemiological data implicate obesity and excess weight as factors associated with an increased risk of premature death (Adams 2006; Katzmarzyk 2003).

According to the National Institutes of Health (NIH) Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, "the initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline." The guidelines further state that, "The rationale for this initial goal is that even moderate weight loss, i.e., 10% of initial body weight, can significantly decrease the severity of obesity-associated risk factors" (NIH 1998).

Despite this target, currently approved pharmacotherapies are generally associated with <5% weight loss and are often poorly tolerated (Padwal 2007). At present, the only treatment demonstrated to reliably produce more than 10% sustained weight loss for obesity is bariatric surgery – an invasive approach associated with nutritional deficiencies, infections, and rarely, death. To avoid the health consequences predicted to result from the obesity epidemic in the United States, new medical approaches, including combination pharmacotherapy of drugs with distinct mechanisms, delivering more effective and better tolerated treatment are needed.

QNEXA Clinical Development Program

The original QNEXA clinical development program for obesity consisted of three Phase 3 studies, four Phase 2 studies and ten Phase 1 studies, which altogether included more than 5,000 subjects. Almost 3,000 subjects were treated with QNEXA for 6 months to 1 year duration. At the time of the original submission, an additional Phase 2 and Phase 3 study were ongoing, and since have been included in the resubmission.

The study population evaluated in the QNEXA pivotal clinical development program included a range of adult subjects, from overweight (BMI >27 kg/m^2) to severely obese (BMI >60 kg/m^2), with a range of obesity-related comorbidities, including type 2 diabetes, hypertension, and hypertriglyceridemia. The program also included subjects with depression or a history of depression. While the majority of subjects in the one year cohort were female (74.1%) and Caucasian (84.1%), the program also included African Americans (13.7%) and a smaller percentage of other races. In this one year cohort, 13.5% of subjects had diabetes; 40.3% had hypertension; 25.8% had hypertriglyceridemia; 20.7% of subjects had a history of depression, and 15% of subjects were taking antidepressants at baseline. At baseline, mean SBP was 126.1 mmHg, mean DBP was 79.4 mmHg, and mean heart rate was 72.5 bpm. Within a total of 3807 patients in the one-year cohort, based on a modified ATP III definition of cardiovascular risk, 752 (19.8%) fell into the "low" risk category, 2498 (65.6%) into

"moderate" risk, and 557 (14.6%) into the "high" risk group. Thus, the QNEXA clinical development program included a population sample of patients representing a broad spectrum of cardiovascular risk, and one that well represents the range of patients likely to use QNEXA, if approved.

The initial selection of the respective doses of the two components in QNEXA was based on documented, published weight loss and tolerability results from studies of the individual agents (Bray 1998; Bray 1999; Bray 2003). These published studies demonstrated that a 100 mg dose of topiramate was tolerable and associated with the maximal weight loss. The proof-of-concept study (OB-201) provided initial evidence that a phentermine/topiramate 15 mg/100 mg combination produced a magnitude of weight loss (~10%) that exceeded levels associated with current pharmacotherapies and surpassed FDA criteria for approval of weight loss agents set forth in FDA Guidance for Industry "Developing Products for Weight Management" (FDA Guidance 2007). Moreover, this combination achieved the recommended target weight loss goal of 10% established by the NIH guidelines.

The design of the pivotal Phase 3 studies were discussed and agreed upon with the FDA through the End-of-Phase 2 meeting and the use of the Special Protocol Assessment process (studies OB-301 and OB-303). The Phase 3 clinical trial program was designed to assess the safety and efficacy of a single-capsule, extended-release formulation containing immediate-release phentermine and extended-release topiramate, and was designed to mimic the time-sequenced daily dosing of the individual components studied in study OB-201. The QNEXA formulation was designed so that peak exposure of each drug was separated by 7 to 8 hours with peak phentermine exposure in the morning and peak topiramate exposure near late afternoon/evening. The delivery of the topiramate component later in the day was expected to provide peak drug exposure for afternoon/evening hunger.

The QNEXA pivotal Phase 3 clinical trial program investigated three dose levels—QNEXA (phentermine/topiramate) Low dose (3.75 mg/23 mg), Mid or recommended dose (7.5 mg/46 mg), and Top dose (15 mg/92 mg)—in severely obese subjects as well as in overweight and obese subjects with comorbidities including type 2 diabetes, hypertension, and hypertriglyceridemia.

Study OB-301 was conducted to demonstrate the contribution of each component to the weight loss effect of QNEXA and enrolled a population of 756 obese adults treated with QNEXA Mid or Top dose, phentermine alone, topiramate alone, or placebo for 28 weeks. Dose-related weight loss was observed. The maximal weight loss observed with the combination was greater, and was achieved at significantly lower doses, than the maximal weight loss observed with either component alone or placebo.

The two pivotal Phase 3 studies (OB-302 and OB-303) were designed in consultation with FDA and in compliance with the FDA Obesity Guidance in terms of the number of subjects treated, the populations enrolled, study duration and design, and the endpoints evaluated. Study OB-302 was a 1-year, randomized, double-blind, placebo-controlled study that enrolled 1,267 obese adult subjects with a BMI of at least 35 kg/m^2 with no upper limit. Both Class II (BMI >35 kg/m^2) and Class III (BMI >40 kg/m^2) subjects were included, with limited obesity-related comorbidities. This study compared QNEXA Low dose and Top dose with

placebo. Study OB-303 was a 1-year, randomized, double-blind study that enrolled 2,487 overweight and obese adult subjects with two or more of the following weight-related comorbid conditions: hypertension, elevated triglycerides, diabetes, fasting blood glucose >100 mg/dL, and/or waist circumference ≥102 cm for men or ≥88 cm for women. This study compared QNEXA Mid dose and Top dose with placebo. In both studies, primary efficacy was assessed via comparisons of percent and categorical weight loss between both QNEXA groups and placebo after 56 weeks of treatment.

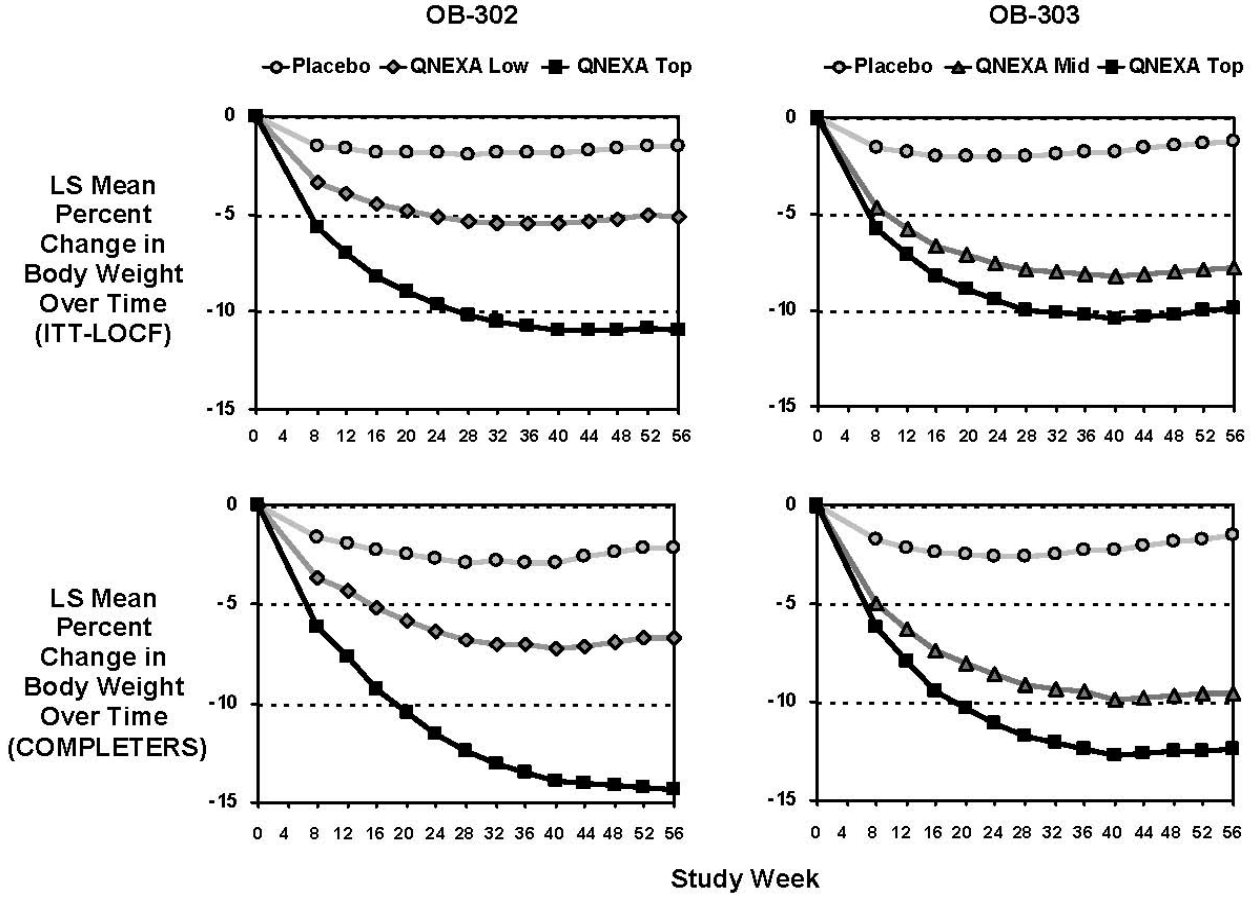
Efficacy in Phase 3 Pivotal Studies

Results across the pivotal Phase 3 studies were consistent with regard to weight loss, including time course of weight loss, as well as proportions of subjects achieving categorical weight-loss benchmarks, and were comparable to the results from the proof-of-concept study (OB-201). Treatment with QNEXA, at all three dose levels, resulted in statistically significant percent and categorical weight loss (from baseline to end of study) compared with placebo treatment. In the ITT-LOCF population, average weight loss achieved in subjects receiving QNEXA Top dose was 10.9% (OB-302) and 9.8% (OB-303), compared with subjects receiving placebo (OB-302, 1.6%; OB-303, 1.2%). Weight loss was also achieved in subjects receiving QNEXA Mid dose (OB-301, 8.5%; OB-303, 7.8%) and Low dose (OB-302, 5.1%).

Significant weight loss with QNEXA was observed at 4 weeks and continued progressively over the course of the 1-year trials **(Figure 1)**. The observed mean and categorical weight loss at 1 year substantially exceeded both FDA and NIH guidance for weight management products. The Phase 3 studies demonstrated a dose response relationship with QNEXA therapy and supported three dosing levels that provide a flexible dose regimen. Subgroup analyses based on subject baseline demographic characteristics indicated that weight loss achieved with QNEXA therapy was unaffected by race, sex, age, baseline BMI or baseline comorbidities. Weight loss with QNEXA was primarily attributed to a reduction in fat mass and not lean body mass and reductions in subject mean waist circumference were consistently greater in subjects treated with QNEXA, relative to placebo, across trials.

Subjects who had completed study OB-302 on drug lost 14.4% of baseline body weight, and subjects who had completed study OB-303 on drug lost 12.4% of baseline body weight **(Figure 1)**. For the QNEXA Low and Mid dose groups, mean percent weight loss progressively increased from baseline to Week 40 and then was relatively stable from Week 40 to the end of the study. Week 56 weight loss for subjects completing study on drug was 6.7% for QNEXA Low dose (OB-302) and 9.6% for QNEXA Mid dose (OB-303). For the placebo groups, mean percent weight loss was relatively stable from Week 28 to the end of the study, with the Week 56 mean percent weight loss averaging 2.1% in OB-302 and 1.6% in OB-303. **Figure 1** shows the mean percent weight loss over time by treatment group for the ITT-LOCF and Completers sets in studies OB-302 and OB-303.

Figure 1. Percent Weight Loss From Baseline Over Time (ITT-LOCF and Completers Sets)



Effects of QNEXA on Weight-related Comorbidities

The effect of QNEXA treatment on important weight-related comorbidities was assessed throughout the clinical program in the whole study population regardless of baseline status, and then specifically, in pre-existing disease populations, such as subjects with hypertension, hypertriglyceridemia, and type 2 diabetes. Significant and dose-related improvements in cardiovascular, metabolic, glycemic and inflammatory endpoints were obtained with QNEXA therapy generated weight loss and maintained throughout the 56 weeks of treatment. QNEXA therapy resulted in weight loss and consistently observed significant improvements from baseline in systolic and diastolic blood pressure, (SBP and DBP, respectively), triglycerides, high-density lipoprotein cholesterol (HDL-C), liver enzymes (ALT), fibrinogen, and C-reactive protein (CRP) across the Phase 3 trials. Hemoglobin A_{1c} (HbA_{1c}), and fasting glucose were also consistently and significantly reduced from baseline, compared with placebo across Phase 3 trials.

In analyses of all subjects treated in study OB-303, both QNEXA Mid and Top dose treatment resulted in significant and clinically meaningful reductions in fasting insulin and insulin resistance. Moreover, among subjects without a diagnosis of type 2 diabetes at study entry,

annualized incidence of progression to type 2 diabetes, based on 2 or more consecutive visits with fasting glucose levels of ≥126 mg/dL or 2-hour post-oral glucose tolerance test [(OGTT)] ≥200 mg/dL, was observed in 30 placebo-treated subjects with an annualized incidence rate of 4.5% compared with 14 subjects in the QNEXA Top dose group with an annualized incidence rate of 1.9%, indicating a 58% decrease in the annualized incidence of new-onset type 2 diabetes in these study subjects due to weight loss.

Analysis of pre-specified subgroups of subjects with hypertension, hypertriglyceridemia or diabetes at baseline in study OB-303 indicated that significant and greater absolute improvements from baseline in cardiovascular, glycemic, metabolic and inflammatory endpoints could be attained due to weight loss in obese QNEXA-treated subjects with disease versus without disease. QNEXA Top dose-treated hypertensive subjects in study OB-303 demonstrated significant and clinically meaningful reductions in SBP (9.1 mmHg) and DBP (5.8 mmHg) compared with placebo-treated hypertensive subjects (SBP, 4.9 mmHg; DBP, 3.9 mmHg). Subjects with hypertriglyceridemia treated with QNEXA Top dose in study OB-303 demonstrated significant and clinically meaningful improvements from baseline in levels of triglycerides (TG) [reduced 25.6%], HDL-C (increased 10.7%), and total cholesterol (TC) [reduced 7.8%], compared with placebo (TG reduced 8.8%; HDL-C increased 2.8%; TC reduced 4.9%).

QNEXA-treated diabetic subjects in study OB-202/DM-230 (long-standing diabetes) and study OB-303 demonstrated significant and clinically meaningful reductions in HbA_{1c} (1.6% in OB-202/DM-230 and 0.4% in OB-303) and other glycemic endpoints, including fasting glucose and post-prandial glucose (measured in OB-202/DM-230).

Assessment of the change from baseline to study endpoint in medications taken by subjects for treatment of hypertension and diabetes revealed that improvements in disease endpoints following QNEXA treatment were also associated with significant concomitant reduction in antihypertensive and antidiabetic medications, compared with placebo. In study OB-303, among the subjects with hypertension, 3.9% and 4.3% of QNEXA Mid dose and QNEXA Top dose subjects, compared to 8.1% of placebo subjects, started new anti-hypertensive medications. Conversely, 10.5% and 14.8% of QNEXA Mid dose and QNEXA Top dose subjects, compared with 4.7% of placebo subjects, discontinued existing anti-hypertensive medications. Among subjects with diabetes in study OB-303, 4.5% of QNEXA Mid dose and 4.3% of QNEXA Top dose-treated subjects, compared with 14.6% of placebo-treated subjects started new antidiabetic medications, while 3.0%, 3.7% and 2.5% of QNEXA Mid dose, QNEXA Top dose and placebo subjects, respectively, discontinued existing antidiabetic medications. Thus, the previously-discussed QNEXA-related improvements in blood pressure and glycemic parameters were observed in patients with these conditions at baseline despite less intensive pharmaceutical management of these parameters in QNEXA-treated subjects compared to placebo-treated subjects.

Assessments of Quality of Life using the Impact of Weight on Quality of Life (IWQOL) and Short Form (SF)-36 (a non-weight related questionnaire) questionnaires during the QNEXA clinical development program indicated significant and greater improvement from baseline in health, daily function, and overall quality-of-life scores in subjects treated with QNEXA compared with subjects treated with placebo.

Safety

General Safety

The overall safety of QNEXA in the original NDA was based primarily on the integrated safety data obtained from the three pivotal Phase 3 studies (OB-301, OB-302, and OB-303) and the two supportive Phase 2 studies (OB-202 and DM-230). The integrated analyses demonstrated that QNEXA Low dose, Mid dose, and Top dose were safe and generally well tolerated by subjects and consistent with the known side effects of phentermine and topiramate. Overall study retention was significantly higher in all 1-year studies for QNEXA treatment arms compared with placebo arms.

The primary analysis of safety was performed on the 1-Year Cohort. The overall incidence of treatment-emergent adverse events (TEAEs) was higher in the active treatment groups than in the placebo group (placebo, 76.0%; QNEXA Low dose, 80.0%; Mid dose, 85.1%; Top dose, 87.2%). Most of the TEAEs were mild or moderate in severity. The incidence of severe TEAEs was greater for QNEXA-treated subjects (placebo, 8.6%; Low dose, 10.4%; Mid dose, 11.0%; Top dose, 12.5%). However, the incidence of treatment-emergent serious adverse events (SAEs) for the 1-Year Cohort was low and similar for the treatment groups (placebo, 3.3%; Low dose, 2.5%; Mid dose, 2.8%; Top dose, 3.6%). One death occurred during the studies: a placebo-treated subject who suffered cardio-respiratory arrest in study OB-303. No differences between QNEXA and placebo treatment in the incidence of SAEs in particular system organ classes, including the cardiac system organ class, were noted.

The most frequently reported TEAEs with QNEXA treatment were paresthesia (17.0%), dry mouth (16.6%), constipation (15.1%), upper respiratory tract infection (13.5%), nasopharyngitis (10.0%), and headache (9.8%). The incidence of paresthesia, dry mouth, constipation, dysgeusia, insomnia, irritability, and alopecia was higher in the active treatment groups than in the placebo group and increased in a dose-related manner. Overall study retention was consistently higher for all QNEXA arms compared with placebo; however, the percentages of subjects who discontinued study drug due to an AE were higher in the active treatment groups than in the placebo group (placebo, 8.5%; Low dose, 11.7%; Mid dose, 11.6%; Top dose, 17.5%).

Targeted Medical Events

The safety and tolerability profile of QNEXA was also evaluated in the context of known adverse effects listed in the FDA approved labeling for topiramate and phentermine. To ensure that these and other AEs of interest (targeted medical events) were clustered and assessed in a comprehensive manner, selected events were identified at the preferred term level and also categorized by class and subclass. The classes of targeted medical events included: psychiatric disorders, which included subclasses of sleep disorders, anxiety, depression, and suicide/self-injury; cognitive disorders, which included subclasses of attention, language, memory impairment, and other cognitive disorders; psychomotor disorders; drug abuse/withdrawal; menstrual disorders; ophthalmic disorders; and cardiac disorders, which included subclasses of cardiac arrhythmia and ischemic heart disease. Subclasses of the psychiatric disorders class included sleep disorders, depression, anxiety, and

suicide/self-injury. Because the CRL for the original QNEXA NDA required an analysis of safety risks potentially associated with small heart rate increases, and an assessment of topiramate's and QNEXA's teratogenic potential, these two topics are discussed separately at some length after the discussion of overall safety.

From the summary of targeted medical events, the incidence of TEAEs clustered and categorized as sleep disorders was higher in the QNEXA Top dose group (10.8%) than in the placebo group (5.7%). Most of the sleep disorder TEAEs were related to insomnia and were mild in severity (placebo, 3.7%; QNEXA Top dose, 6.2%).

The incidence of TEAEs in the depression (standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ]) subclass, which included affect lability, apathy, crying, depressed mood, depression, dysthymic disorder, mood altered, and tearfulness, was higher in the QNEXA Top dose group (7.7%) than in the placebo group (3.4%); the incidence of TEAEs in the depression subclass was similar for the QNEXA Mid dose group (3.8%) and placebo group (3.4%). None of the depression TEAEs in the 1-Year Cohort was considered to be an SAE. The incidence of moderate or severe depression and depressed mood were similar between treatment groups. There was no difference in the use of new psychiatric or antidepressant medications during the study between active treatment groups and placebo.

The incidence of TEAEs in the anxiety subclass was higher in the QNEXA groups than in the placebo group (placebo, 2.6%; Low dose, 4.6%; Mid dose, 4.8%; Top dose, 7.9%). None of the anxiety TEAEs in the 1-Year Cohort was considered to be an SAE.

There were no attempted or successful suicides, or SAEs of suicidality reported in QNEXA program. The effect of QNEXA on suicidality was thoroughly investigated by prospectively applying two validated tools (CSSRS, PHQ-9) at every visit and by collecting relevant adverse events. Analyses of all the data using these tools revealed no apparent signal of suicidal behavior associated with QNEXA.

There were no serious adverse events reported for the cognitive disorders class. The incidence of TEAEs categorized as cognitive disorders, including the incidence of attention TEAEs and memory impairment TEAEs, was higher in the QNEXA Top dose group (3.5% and 2.5%, respectively) and Mid dose group (2.0% and 1.8%, respectively) than in the placebo group (0.6% for each disorder). The incidence of language TEAEs and other cognitive disorders was low overall but higher in the QNEXA Top dose group (1.2% and 1.8%, respectively) than in the placebo group (0.1% and 0.3%, respectively). The TEAEs categorized as cognitive disorders were primarily mild in severity.

Laboratory Abnormalities

Overall, there were no differences between QNEXA groups and placebo groups in incidence of serious laboratory-related AEs or study drug discontinuations due to laboratory-related AEs. Consistent with FDA-approved prescribing information for Topamax (topiramate) regarding hyperchloremic, non-anion gap, metabolic acidosis, some differences among the treatment groups in changes in safety laboratory parameters of potassium (K+) and bicarbonate were noted. In the 1-Year Cohort, the percentage of subjects with persistent (two

consecutive visits below the given threshold or a value below the given threshold at the final visit) serum bicarbonate values <17 mEq/L was higher in the QNEXA (Low dose, 1.3%; Mid dose, 0.2%; Top dose, 0.7%) treatment groups than in the placebo group (0.1%). Given that the risk for metabolic acidosis increases with reductions in serum bicarbonate and can be compounded by co-medications, the risk for metabolic acidosis with QNEXA in the presence of metformin was investigated. No increased risk for metabolic acidosis was found when QNEXA was co-administered with metformin.

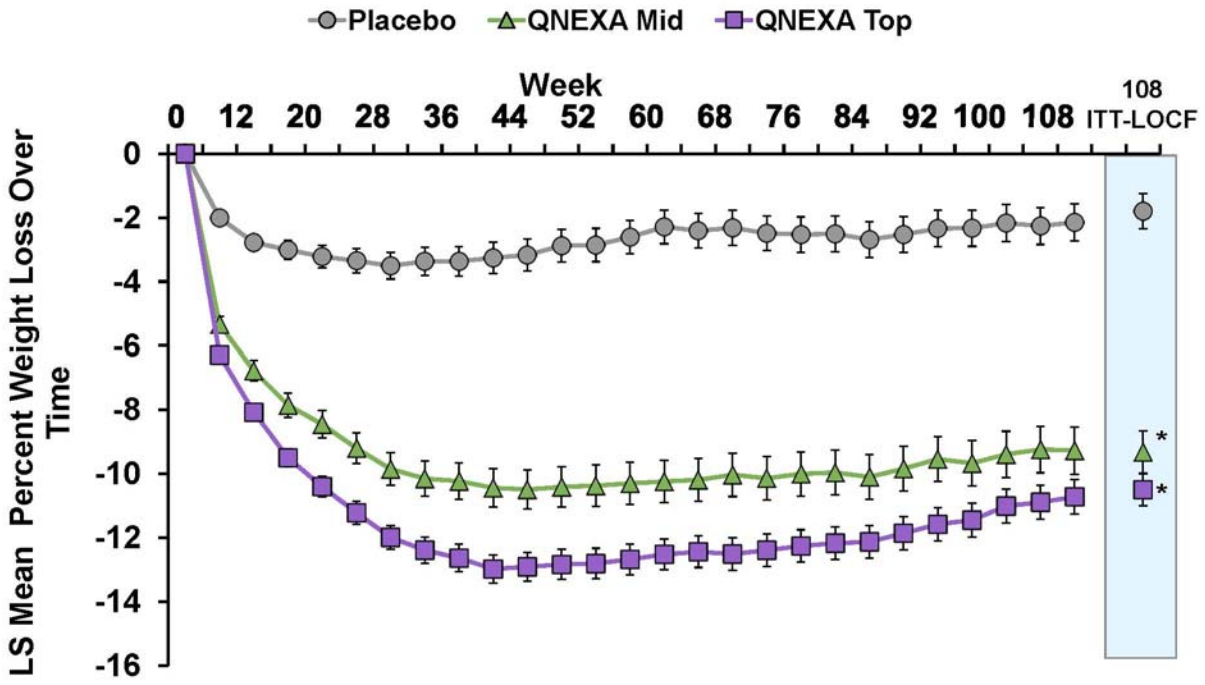
No subject in the placebo or QNEXA Low dose groups and few subjects in the QNEXA Mid (0.2%) and Top (0.1%) dose groups had persistent serum potassium values <3.0 mmol/L concurrent with a decrease of >0.5 mmol/L from baseline. These effects were dose related, were consistent with topiramate's inhibitory effects on carbonic anhydrase enzymes, and occurred only in patients who were treated concurrently with non-potassium sparing diuretics. Overall, decreases in ALT and AST values compared to baseline were observed across the Phase 3 program. Two subjects (one on QNEXA and one on placebo) had elevations in liver transaminases in the presence of elevated bilirubin that occurred concurrently with SAEs of cholelithiasis, which resolved on treatment. Cholelithiasis may result from rapid weight loss.

Extended Safety and Efficacy – Two-Year Cohort

Study OB-305, a double-blind, placebo-controlled, 1-year extension to study OB-303 collected additional long-term safety and efficacy data on QNEXA Mid dose and Top dose during a second year of exposure of obese subjects with obesity-related comorbidities enrolled at selected sites. This study was ongoing at the time of the original 2009 QNEXA NDA submission and the 2010 QNEXA EMDAC meeting and was therefore not included in earlier discussions. The results of study OB-305 were included in the recent QNEXA NDA resubmission.

Study OB-305 was designed to assess the long-term impact of QNEXA-mediated weight loss and maintenance of weight loss on metabolic and cardiovascular comorbidities, particularly the progression to type 2 diabetes. Subjects who elected to enroll in this extension study continued on the same double-blind treatment they were randomized to in study OB-303 for up to 52 weeks of additional exposure. In total, 676 of the 866 eligible subjects enrolled in the study and 574 (84.9%) subjects completed the study. Study OB-305 demonstrated maintenance of significant weight loss with QNEXA after two years of treatment. Average weight losses of 10.5% and 9.3% were achieved at Week 108 with QNEXA Top dose and QNEXA Mid dose, respectively, compared to 1.8% with placebo. At the Week 108 time point, the dose-related effects of QNEXA were still observed, with QNEXA Top dose and QNEXA Mid dose resulting in significantly greater percent weight loss than placebo **(Figure 2)**.

Figure 2. Percent Weight Loss from Baseline Over Time – Study OB-305 (Completer Population and ITT-LOCF)



*p<0.001 versus placebo; Week 0 = date the last measurement obtained on or before the first dose date of double-blind study drug in Study OB-303.
Completer Population = all observed data for subjects still on drug at the reported time point; ITT-LOCF = intent-to-treat–last observation carried forward; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid 7.5 mg/46 mg; QNEXA Top 15 mg /92mg.

As with the one-year studies, results in important weight related secondary endpoints such as waist circumference, SBP, DBP, and lipid levels were improved with QNEXA treatment at two years. Clinically meaningful improvements in fasting insulin, OGTT glucose and insulin excursions, and insulin resistance were observed with QNEXA treatment relative to placebo after two years of treatment. Based on the American Diabetes Association's criteria of consecutive laboratory thresholds, the annualized incidence of new onset of type 2 diabetes in the two year cohort was lower in the QNEXA groups (QNEXA Top dose, 0.9%; QNEXA Mid dose, 1.7%) than in the placebo group (3.7%), indicating a 76% decrease in the annualized incidence of new-onset type 2 diabetes when comparing Top dose to placebo.

Overall mean exposure to study drug for the 2-Year Cohort was 728.5 days, and overall median exposure to study drug was 756.0 days. The exposure to study drug was similar for each treatment group. The majority of subjects in each treatment group had more than 104 weeks of exposure to study drug.

No important differences were observed between the 1-Year and 2-Year Cohorts in the types of TEAEs or incidence of specific TEAEs with QNEXA treatment, indicating that long-term treatment did not result in any new types of AEs or substantially increased rates of AEs.

In total, 637 (94.4%) subjects in the 2-Year Cohort had a TEAE during studies OB-303 and OB-305. The overall incidence of TEAEs was 96.0% in the placebo group, 92.8% in the QNEXA Mid dose group, and 93.9% in the QNEXA Top dose group. Most of the TEAEs were mild or moderate in severity. A greater percentage of subjects in the QNEXA Top dose group than in the placebo group had a TEAE that was severe in severity. The percentages of subjects with mild TEAEs were similar for the treatment groups.

No subjects died during study OB-305. In total, 47 (7.0%) subjects had a treatment-emergent SAE: 14 (6.2%) subjects in the placebo group, 9 (5.9%) subjects in the QNEXA Mid dose group, and 24 (8.1%) subjects in the QNEXA Top dose group. No subjects had a treatment emergent SAE that was considered by the investigators to be related to study drug.

In total, 27 (4.0%) subjects discontinued study drug in study OB-305 due to a TEAE in studies OB-303 and OB-305. The percentage of subjects who discontinued study drug due to a TEAE was similar for the treatment groups. In total, 11 (1.6%) subjects discontinued study drug due to a drug related TEAE.

Cardiovascular Safety

The QNEXA Complete Response Letter ("CRL") requested that VIVUS "[p]rovide evidence that the elevations in heart rate associated with phentermine/topiramate do not increase the risk for major adverse cardiovascular events."

Heart Rate and Blood Pressure Effects Across QNEXA Program and By Subgroups

In the 1-Year Cohort, small and dose-related mean increases in heart rate were observed in the QNEXA treatment groups (QNEXA Low dose, 1.3 bpm; QNEXA Mid dose, 0.6 bpm; QNEXA Top dose, 1.6 bpm) compared with placebo treatment groups (no change). The actual increase in heart rate was only significant compared to placebo for the Top dose. Mean decreases in SBP and DBP were observed for all of the treatment groups. The mean decreases in SBP were larger for the QNEXA groups than for the placebo group. The mean decreases in DBP were larger for the QNEXA Top dose group and QNEXA Mid dose group than for the placebo group.

A thorough evaluation of heart rate and blood pressure changes across various subgroups of the study population were performed to identify whether or not patients who were at higher baseline risk also experienced greater increases in heart rate. These analyses demonstrated that the small heart rate increases observed overall were consistent across age, race, and ATP-III risk strata, and importantly, were not amplified in patients with hypertension or diabetes. The only significant predictor of heart rate increases was baseline heart rate, where the largest heart rate increases from baseline were observed in patients with the lowest baseline heart rate values. Importantly, while heart rate changes were highly consistent across risk subgroups, blood pressure reductions tended to increase in higher risk segments of the population, particularly among patients with hypertension at baseline. Collectively, these subgroup analyses indicate that patients who are at higher baseline risk experienced if anything, a less adverse pattern of changes in heart rate and blood pressure.

In sleep apenea patients, in contrast with the morning "spot" measures of heart rate in the Phase 3 program, mean overnight (8 hours) heart rate at Week 28 was significantly reduced by 4.8 bpm from baseline in subjects treated with QNEXA 15 mg/92 mg and by 3.3 bpm from baseline in subjects treated with placebo. Thus, in subjects treated with QNEXA 15 mg/92 mg, the deceleration in heart rate observed at night is at least as large; if not larger than for placebo-treated subjects.

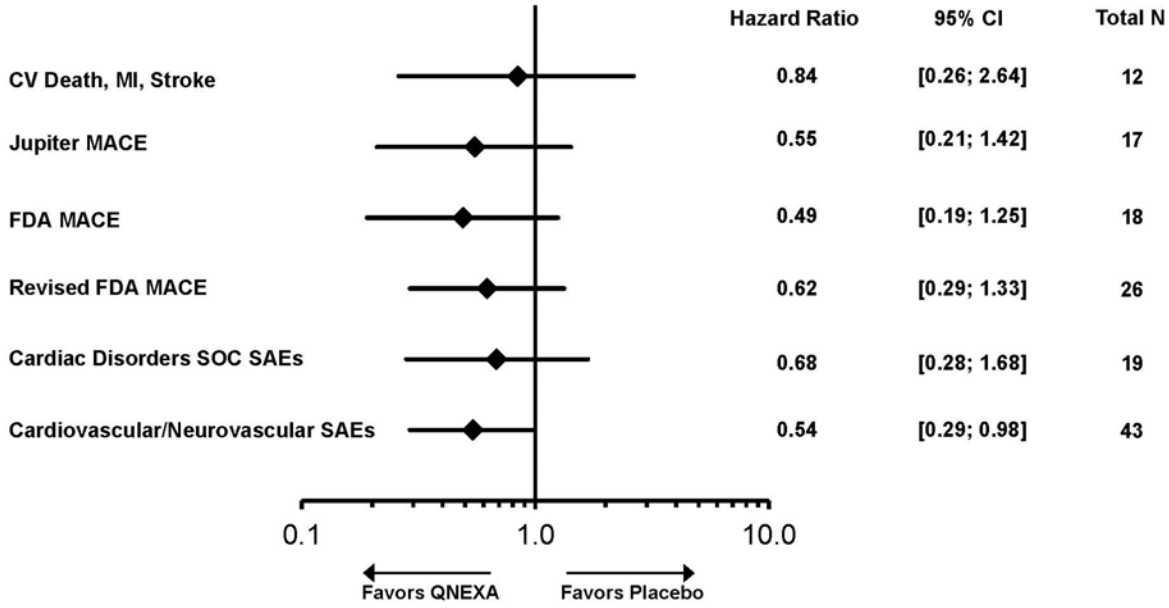
Cardiovascular Adverse Events

VIVUS examined whether increased heart rate had any significant impact on cardiac arrhythmias. Evaluation of the incidence of TEAEs in the cardiac arrhythmia subclass demonstrated a higher frequency of events in the QNEXA Top dose group (4.7%) and Mid dose group (4.2%) than in the placebo group (1.8%). This observed dose response, however, was accounted for almost entirely by increases in events that are not true arrhythmias. Palpitations, increased heart rate, and tachycardia represented the majority of cardiac arrhythmia TEAEs in the 1-Year Cohort. Palpitations and increased heart rate are expected and dose-related side effects of phentermine. The cardiac arrhythmia TEAEs were primarily mild or moderate in severity and were serious for 4 (0.3%) subjects in the placebo group, 2 (0.4%) subjects in the Mid dose group, and 2 (0.1%) subjects in the Top dose group. Importantly, an examination of clinically meaningful arrhythmias showed no difference between treatment groups.

VIVUS has reviewed the limited number of MACE events available from existing studies of QNEXA as well as other cardiac safety information important to an assessment of MACE risk. These events are summarized into composite analyses from the narrowest, cardiovascular death, MI, and stroke, to the most broad composite, based on all cardiovascular and neurovascular events within several SOCs **(Appendix 5)**. The various composites along with hazard ratio and confidence intervals are summarized below **(Figure 3)**. Also presented are the numbers of events within each category for the placebo and QNEXA total groups.

Across the different composites of major CV outcomes evaluated, hazard ratios (QNEXA versus placebo) did not exceed 1.0 and were relatively consistent, ranging from 0.49 for the FDA MACE endpoint to 0.84 for the endpoint of cardiovascular death, MI, and stroke. For all composite outcome endpoints, the 95% confidence interval of the hazard ratio had an upper bound ranging from 0.98 for the broadest composite, including all neurovascular and cardiovascular events, up to 2.64 for the narrowest definition including CV death, stroke and MI.

Figure 3. Relative Risk of Major Cardiovascular Events – (Safety Set)



Cardiovascular Discussion and Conclusions

A previous example of an obesity therapy, sibutramine, which increased heart rate and blood pressure, was found to be associated with a small but statistically significant increase in the incidence of major cardiac events. In contrast, the small heart rate increases associated with QNEXA occurred in conjunction with significant decreases in systolic and diastolic blood pressure. Moreover, analyses of effects on the rate-pressure product (RPP), which is defined as the product of heart rate (bpm) and SBP (mmHg) divided by 1,000, and is a measure that has been shown to correlate with myocardial oxygen demand (White 1999) shows QNEXA to be associated with reductions, rather than increases in RPP. For the 1-Year Cohort, statistically significant mean reductions in RPP were observed in the placebo, QNEXA Mid dose, and QNEXA Top dose groups. None of the comparisons between placebo and QNEXA treatment groups for change in RPP were statistically significant. The comparison of mean change in RPP between the placebo group and the QNEXA Top dose group was significant. While these changes may not be large, they at least provide assurance that the increase in heart rate observed with Qnexa is not associated with an increase in myocardial oxygen demand, an important putative mechanism by which increased heart rate may lead to more serious cardiac events.

Analyses of the small number of major adverse cardiovascular events within the clinical program using multiple accepted criteria do not suggest an increased frequency of events compared to placebo. In patients who did experience major events, there does not appear to be any consistent pattern of heart rate increases preceding these events. When the overall effects of QNEXA are evaluated with validated risk models such as the Cooper Clinic Mortality Risk Index (which include heart rate), the beneficial effects of QNEXA on BMI, blood pressure, and diabetic status, outweigh any potential adverse effects of a small increase on heart rate.

Thus, in consideration of the overall absence of excess major adverse cardiovascular events in subjects in the QNEXA clinical program, the lack of a direct relationship between major adverse cardiovascular events and heart rate changes, the beneficial effects of QNEXA on metabolic and cardiovascular risk factors, VIVUS believes that sufficient cardiovascular safety data exist to support the approval of QNEXA.

Teratogenicity

The current topiramate prescribing information includes a warning regarding teratogenicity and carries a Pregnancy Category D designation indicating that despite evidence of fetal risk, the use of the drug may still be acceptable in pregnant women based on its potential benefits in epilepsy and migraine prevention. Based largely on topiramate (TPM) data, the QNEXA CRL requested that VIVUS "[p]rovide a comprehensive assessment of topiramate's and [QNEXA's]'s teratogenic potential."

Data at the time of the CRL indicated that the prevalence of all major congenital malformations (MCMs) in the North American Antiepileptic Pregnancy Registry (NAAPR) was 3.8% (11/289 exposed pregnancies) with a relative risk of 2.8 (95% CI, 1.0–8.1) compared to untreated controls (Hernandez-Diaz 2010). Four of the 11 MCMs were oral cleft (OC), two of which were isolated cleft lip. The prevalence of OC was 1.4%, compared to a prevalence of 0.07% in infants of mothers without epilepsy or treatment of other AEDs. The relative risk of oral cleft in topiramate exposed pregnancies was 21.3 (CI, 7.9-57.1) (FDA Safety Communication 2011). The most recent results from the NAAPR include updated rates of MCMs observed with various AEDs, 3.4% (11/321) for topiramate (Hernandez-Diaz 2011). This registry also used MCM rates associated with lamotrigine as a reference group for all other AEDs. Compared to lamotrigine, the relative risk of MCMs was 1.8 (0.9–3.6) for topiramate and 4/321 infants exposed to topiramate (1.3%) had oral clefts.

Since the initial NDA submission, the prevalence of MCMs with topiramate exposure has been examined in three additional separate studies. A recent population study of all births in Denmark (837,795 infants) over a 12-year period revealed that the adjusted prevalence odds ratio for MCM following first trimester exposure to topiramate (versus no AED exposure) was 1.44 (95% CI, 0.58–3.58) (Molgaard-Nielsen 2011). In a case-control study from the BDS and NBDPS surveillance programs, a total of 33,825 MCMs were evaluated, and the adjusted odds-ratio for topiramate (versus no AED) exposure between women giving birth to infants with a MCM compared to women giving birth to non-malformed infants was 1.01 (95% CI, 0.37–3.22) (Margulis 2011). Lastly, in the retrospective cohort study from the Wolters Kluwer Pharma Solutions Source® Lx Patient Longitudinal claims database, relative risk values for patients exposed to topiramate during the first trimester of pregnancy, compared to various control groups designed to match patients by diagnosis, ranged from 0.87 (95% CI, 0.59–1.29) for the comparison with patients with a diagnosis of epilepsy, to 1.32 (95% CI, 0.88–1.97) for the comparison with patients exposed to other AEDs. This study also indicated that the MCM prevalence following first trimester topiramate exposure may be lower than the prevalence in patients with a diagnosis of diabetes (RR 0.61; 95% CI, 0.43–0.87) which itself is associated with increased prevalence of a wide variety of congenital malformations.

The retrospective cohort study using Wolters Kluwer claims data demonstrated prevalence rates for OC of 0.23% following first trimester topiramate exposure, compared to prevalences that ranged from 0.16% to 0.31% across the various comparator cohorts. These prevalence rates are fairly close to the expected background prevalence of approximately 0.15%, and far under the prevalence initially identified in the NAAPR study (1.4%). While the prevalence in the TPM cohort was not significantly higher than the prevalence in any of the comparator cohorts, observed upper bounds for the 95% confidence intervals of relative risks between cohorts ranged from 3.7 to 6.9. While this study did not show significant differences between cohorts, it was not able to exclude a signal. The combined data from the BDS and NBDPS surveillance programs demonstrated 7 TPM exposures among 3,034 women delivering infants with cleft lip and cleft palate compared to 6 exposures among 15,367 women giving birth to non-malformed infants, which yielded an adjusted odds-ratio of 5.36 with a 95% CI of 1.49−20.07.

VIVUS is currently performing the FORTRESS study, a retrospective observational study utilizing existing electronic healthcare databases to assess fetal outcomes in the offspring of women who were exposed to topiramate during the first trimester of pregnancy. The FORTRESS study identified approximately 2,000 topiramate exposed mother-infant dyads, of whom 1,740 were exposed to topiramate monotherapy, and is believed to be the largest retrospective topiramate medical claims study ever completed. The study will evaluate the relative risks of oral clefts (OC) and major congenital malformations (MCM) in the offspring of women exposed to topiramate during pregnancy as compared to a control group that had prior exposure to topiramate or othe AEDs, but no exposure during pregnancy (the Formerly Exposed [FE] cohort). Early FORTRESS results indicate that the oral cleft prevalence associated with oral topiramate monotherapy in the first trimester of pregnancy was 0.29% compared with 0.16% for the FE cohort. The OC prevalence ratio for the TPM monotherapy sub-cohort versus FE cohort standardized by center-specific propensity score decile was 2.00 (95% CI, 0.71−5.68).

In summary, the most recent studies conducted to date indicate that topiramate exposure during the first trimester of pregnancy has no effect on the prevalence of MCMs overall, but may result in an increase of approximately 2-fold (based on two cohort-control studies) and up to 5-fold (based on case-control studies) in the prevalence of oral clefts, and support existing topiramate prescribing information. The small numbers of events, however, limit the ability to quantify the relative risk more accurately.

Analyses of data on all major congenital malformations is in process, and will be made available once final validated results have been obtained. The study will be completed in the second half of 2012. Final results from the FORTRESS study are expected to provide a more statistically precise estimate of effect than previous studies.

Risk Mitigation Strategy for QNEXA

VIVUS has designed a comprehensive risk management program focusing on the risk of teratogenicity with exposure to QNEXA in women of childbearing potential (WOCBP). This program was designed through collaboration with the FDA, and key aspects include labeling, a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide, a

Communication Plan, and Elements to Assure Safe Use (ETASU) for healthcare provider training and pharmacy certification within the QNEXA pharmacy distribution network. There will also be an implementation system and assessments included in the REMS. In addition to these activities, VIVUS will work with the FDA to implement additional measures to focus on improving contraceptive counseling and compliance, monthly pregnancy testing, data collection on pregnancies which occur on QNEXA, and the provision of additional educational tools for patients and providers focused on supporting safe use. For context, topiramate does not currently have a REMS, but does include a Medication Guide with the package labeling.

Post-Marketing Commitments

VIVUS is currently exploring the feasibility of conducting an active surveillance safety study through a health maintenance organization to monitor for the occurrence of pregnancies and pregnancy outcomes in WOCBP as well as major adverse cardiovascular events (MACE) in men and women using QNEXA in the post-approval setting. The study will compare the occurrence of these outcomes to a control cohort matched for certain baseline characteristics (i.e., age, BMI, and gender) not treated with QNEXA. The goal of this surveillance study is to provide periodic assessment of these outcomes of interest for enhanced pharmacovigilance. If feasible, VIVUS plans to implement such a study at the time of launch of QNEXA with results available 12 months thereafter.

VIVUS also plans to conduct a post-approval superiority cardiovascular outcome trial (CVOT) to evaluate the effect of long-term treatment with QNEXA on the incidence of nonfatal MI, nonfatal stroke, or cardiovascular death and other relevant efficacy and safety endpoints in obese subjects with cardiovascular disease or cardiovascular disease risk factors **(Appendix 4)**.

Conclusions

Current pharmacotherapies used in conjunction with diet and exercise can achieve weight loss of approximately 5%, while surgical interventions, which can achieve >15% weight loss, are invasive and may involve postsurgical complications, including death. There is no available, non-invasive medical treatment that is capable of achieving a long-term meaningful degree of weight loss of ≥10%. There is, therefore, a treatment gap for non-invasive therapies that achieve weight loss in the range of 5% to 15%.

QNEXA is a combination drug product in an extended-release formulation comprised of lower than approved doses of two approved agents (phentermine and topiramate) that produce weight loss through unique and complementary mechanisms. The weight loss response with the combination is greater, and is achieved at significantly lower doses, than the maximal response attained with either agent alone.

QNEXA is highly effective for weight loss across a broad population of overweight and obese subjects, with a similarly broad range of obesity-related comorbidities. Both by measures of central tendency and response rates for various degrees of weight loss from baseline, QNEXA was found to be markedly effective in a high proportion of subjects in promoting durable

weight reduction and in ameliorating the course of obesity-related comorbidities. The proportion of QNEXA-treated subjects attaining ≥10% total body weight loss was comparable across increasing BMI categories at baseline up to a BMI >50 kg/m^2. The benefits of weight reduction with QNEXA treatment on cardiovascular, metabolic, and glycemic parameters were greatest for subjects with the most marked disease characteristics at baseline.

QNEXA treatment was safe and generally well tolerated by overweight and obese subjects with and without weight-related comorbidities. The most commonly observed adverse events, notably paresthesia, dry mouth, dysgeusia, and insomnia, are well known and characterized side effects of one or the other component agent and do not represent novel side effects engendered through the combined pharmacology of the two drugs. Similarly, small increases in the incidence of psychiatric and cognitive effects, primarily observed for the Top dose are known effects of topiramate and were driven predominately by mild to moderate events. These events occurred early and resolved without sequelae. There were no serious psychiatric or cognitive events reported for QNEXA-treated subjects. Importantly, there was no signal for suicidality as assessed with specifically designed psychometric tools throughout the clinical program.

For obese individuals, the adverse impact of obesity on health and quality-of-life outcomes is well documented. Based on the results of the IWQOL and SF-36 questionnaires conducted in support of the QNEXA NDA, durable weight loss and substantial improvements in weight-related comorbidities resulted in significant improvement in health-related and quality-of-life outcomes for QNEXA-treated subjects.

The two safety concerns raised in the CRL have been adequately addressed and do not present an unreasonable risk to obesity patients. Small increases in heart rate associated with QNEXA are not of a magnitude associated with clinically meaningful cardiovascular risk, do not correlate with cardiac event data and are offset by improvements in SBP and DBP as well as other obesity-related comorbidities. Similarly, the teratogenic potential of topiramate has been managed for years through product labeling in seizure and migraine patients. QNEXA will be available with a risk mitigation program designed to inform prescribers, pharmacists, and patients about the potential serious risks of fetal exposure to QNEXA during pregnancy. The risk mitigation program will include labeling, REMS, as well as proposed voluntary measures, which will be finalized with the FDA.

Any risk from QNEXA's effect on heart rate is small and manageable in the context of demonstrated durable weight loss of greater than 10% at the end of two years. In a recent pooled analysis of 1.46 million adults who had never smoked, even modest increases in BMI above 30 kg/m^2 were associated with significant increases in 10-year all-cause and cardiovascular mortality. Using subjects with a BMI of 22.5 to 25.0 as the reference group, the Cox-proportional hazard ratio for all-cause mortality in women was 1.44 for subjects with a BMI of 30.0 to 34.9; 1.88 for those with a BMI of 35.0 to 39.9; and 2.51 for those with a BMI of 40.0 to 49.9. Similar increases in hazard ratios were observed in men. For cardiovascular mortality, the increased risk associated with obesity was even more dramatic, with 10-year hazard ratios of 2.04 for subjects with a BMI of 30.0 to 34.9; 3.05 for those with a BMI of 35.0 to 39.9; and 4.42 for those with a BMI of 40.0 to 49.9 (Berrington de Gonzalez 2010). The mean BMI at baseline of subjects in the QNEXA 1-Year Cohort was 38. Thus, the

treatment population was subject to a two-fold increase in the risk of all-cause mortality and to a three-fold increase in the risk of cardiovascular mortality. The weight-loss benefits of QNEXA (demonstrated to be associated with favorable changes in blood pressure, lipids, insulin sensitivity, markers of inflammation, and reduction in waist circumference in the QNEXA investigational program) are significant and expected to confer major health benefits to patients that VIVUS believes outweigh the small heart rate elevations seen in the Phase 3 program.

QNEXA represents a significant advancement in the medical treatment of obesity and management of weight-related comorbidities, such as hypertension, type 2 diabetes, and dyslipidemia. The ability of QNEXA to produce durable weight loss can be expected to contribute significantly toward ameliorating some of the consequences of obesity and weight-related comorbidities. On the basis of the efficacy and safety data from clinical studies, QNEXA demonstrates a favorable benefit-risk profile when used as an adjunctive measure in the management of obesity.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADA	American Diabetes Association
AE	adverse event
AED	anti-epileptic drugs
AHI	apnea/hypoxia index
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	Analysis of Covariance
APMDs	acute and preventative migraine drugs
AST	aspartate transaminase
ATP III	Adult Treatment Panel III
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time zero to infinity
BDS	Slone Epidemiology Center Birth Defects Study
BID	twice daily
BMI	body mass index
BP	blood pressure
Bpm	beats per minute
BrAC	breath alcohol concentration (level)
CDC	Center for Disease Control and Prevention
CCMRI	Cooper Clinic Mortality Risk Index
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase myocardial band
cm	Centimeter
C_{max}	peak plasma concentration
CNS	central nervous system
CVOT	cardiovascular outcome trial
Cr_{cl}	creatinine clearance
CRL	complete response letter
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
CV	cardiovascular

CVA	cerebrovascular accident
CVD	Cardiovascular disease
CYP	cytochrome P450 (enzyme)
DBP	diastolic blood pressure
D/C	discontinued
DEXA	dual energy x-ray absorptiometry
DM	Diabetes mellitus
ECG	electrocardiogram
EEG	electroencephalogram
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
ET	early termination
ETASU	Elements to Assure Safe Use
F	Fahrenheit
FE	Formerly Exposed
FORTRESS	Fetal Outcome Retrospective TopiRamate ExpoSure Study
FDA	Food and Drug Administration
HbA_{1c}	hemoglobin A_{1c}
HCl	hydrochloride
HCP	healthcare provider
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment of insulin resistance
HR	Hazard Ratio
HS	High-sensitivity
hs-CRP	high-sensitivity–C-reactive protein
IMS	Information Management System
INR	international normalized ratio
ITT	intent-to-treat (population)
IU/L	international units per liter
IWQOL	Impact of Weight on Quality of Life Questionnaire
K/µL	thousands per microliter
Kg	kilogram
kg/m^2	kilogram per meter squared (unit of measure for body mass index)
LDL-C	low-density lipoprotein cholesterol
LEARN®	Lifestyle, Exercise, Attitudes, Relationships and Nutrition

LFT	liver function test
LOCF	last observation carried forward (analysis)
LS	least squares
MACE	major adverse cardiac event
MAO	monoamine oxidase
MCM	major congenital malformation
µg	Microgram
µIU/mL	micro-international units per milliliter
mEq/L	milliequivalent per liter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/day	milligrams per day
mg/dL	millgrams per deciliter
mg/L	milligrams per liter
mL	milliliter
mL/min	milliliter/minute
MI	myocardial infarction
mmHg	millimeter mercury
mmol	millimoles per liter
MRI	magnetic resonance imaging
msec	millisecond
NA	not available
NAAPR	North American Antiepileptic Pregnancy Registry
NBDPS	Center for Disease Control's National Birth Defects Prevention Study
NDA	New Drug Application
ng/mL	nanograms per milliliter
NIH	National Institutes of Health
NOS	not otherwise specified
NNT	number needed to treat
OB	Obesity
OC	oral cleft
OGTT	oral glucose tolerance test
OR	odds ratio

OSA	obstructive sleep apnea
P	placebo
PD	Pharmacodynamic
PHQ-9	Patient Health Questionnaire
PHEN	phentermine
PK	pharmacokinetic
PMD	preventative migraine drugs
popPK	population PK
PR	The period in the tracing of the electrocardiogram between the start of the P wave and end of the R wave
QD	once daily
QNEXA Top	The oral, fixed-dose combination of VIVUS's proprietary capsule formulation of phentermine (15 mg) and topiramate (92 mg)
QNEXA Mid	The oral, fixed-dose combination of VIVUS's proprietary capsule formulation of phentermine (7.5 mg) and topiramate (46 mg)
QNEXA Low	The oral, fixed-dose combination of VIVUS's proprietary capsule formulation of phentermine (3.75 mg) and topiramate (23 mg)
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RDI	respiratory disturbance index
REMS	Risk Evaluation and Mitigation Strategies
RPP	rate-pressure product
RR	relative risk
SAE	serious adverse event
SBP	systolic blood pressure
SCOUT	Sibutramine Cardiovascular Outcomes Trial (SCOUT).
SD	standard deviation
SE	standard error
SF-36	Short Form-36
SMQ	standardized Medical Dictionary for Regulatory Activities (MedDRA) query
SOC	system organ class
SPA	Special Protocol Assessment
ST	segment in the tracing of the electrocardiogram between the start of the S wave and the end of the T wave
TC	total cholesterol
TEAE	treatment-emergent adverse event

TG	triglycerides
TIA	transient ischemic attack
TID	Three times daily
T_{max}	time to peak plasma concentration
TME	targeted medical event
Tmt	Treatment
TPM	Topiramate
U/L	units per liter
ULN	upper limit of normal
U. S.	United States
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 Need for Effective Pharmacotherapy to Treat Obesity

National Health and Nutrition Examination Survey data from 2007-2008 indicate that approximately 68% of U.S. adults are obese or overweight, and one-third of adults have a body mass index (BMI) ≥30 kg/m^2 (Flegal 2010). Individuals with a BMI between 30 and 40 kg/m^2 lose between 1 and 7 years of life expectancy, and those with a BMI >45 kg/m^2 lose up to 13 years (Fontaine 2003). Obesity's association with increased risk of premature death is primarily caused by a variety of comorbidities, including dyslipidemia, cardiovascular disease, hypertension, cancer, and type 2 diabetes (Flegal 2007; Must 1999; Poirier 2006). Even modest weight loss of 5% to 10% can result in a marked improvement in obesity-related metabolic and cardiovascular risk factors (Goldstein 1992; Pasanisi 2001; Douketis 2005).

Diet, exercise, and behavior modification without pharmacologic enhancement have demonstrated limited efficacy in treating obesity. The complex biology of obesity may explain varying responses to obesity therapies across populations of obese patients, and failure of most obese individuals to achieve sustained weight reduction without supplemental pharmacologic or surgical intervention. Further complicating the obesity care landscape, several attempts at development of pharmacotherapy have resulted in the marketing and subsequent withdrawal of drugs with unacceptable risks and only modest weight loss benefit. Most recently, sibutramine was withdrawn from the U.S. Market in October 2010 after clinical trial data demonstrated that the drug increased adverse cardiovascular outcome events.

The two FDA-approved oral medications currently marketed in the U.S. for treatment of obesity are associated with low to moderate weight loss, are often poorly tolerated, are transiently efficacious, and exhibit variable responses among patients.

- *Orlistat* was approved in 1999 and 2007 in prescription and over-the-counter formulations at 120 mg and 60 mg TID, respectively. Orlistat achieves a mean placebo-adjusted weight loss of 3% to 4% at 1 year. Extension of therapy to 2 years results in the regain of one-third of the lost weight. Orlistat is also associated with substantial gastrointestinal side effects that limit its use.

- *Phentermine* was first approved in 1959 and, at its recommended dose of 37.5 mg/day (phentermine hydrochloride weight; equivalent to 30 mg phentermine free base), achieves a mean weight loss of 6% to 7% (Hendricks 2011). Phentermine is only approved for short-term (up to 3 months) use. Despite modest efficacy and limitations on duration of use, phentermine is the most widely prescribed weight loss agent in the U.S. Several new formulations of phentermine have been approved for weight loss as recently as June 2011.

Current FDA guidance notes that efficacy of weight loss products can be established by a demonstration, after one year of treatment, that the difference in mean weight loss from baseline in the treatment group versus the placebo group is at least 5 percent and is statistically significant; or that the proportion of subjects who lose at least 5 percent of

baseline body weight in the treatment group is at least 35%, is approximately double the proportion in the placebo group and that the difference between groups is statistically significant. While several pharmacotherapies have met these requirements, to date no oral agent has demonstrated a significantly higher threshold of weight loss or compelling evidence of beneficial long-term outcomes in obesity. Greater and more lasting weight loss of 16% to >30% has been achieved with various invasive bariatric surgery procedures, with concomitant reductions in related comorbidities and mortality. Additional risks, patient eligibility considerations, and the need for significant lifestyle modifications, however, limit the broad applicability of such procedures (Colquitt 2009).

New non-invasive therapies are needed to fill the existing treatment gap between current pharmacotherapies providing <5% weight loss and bariatric surgery. An oral therapy that can affect multiple mechanisms may improve efficacy, increase the probability that patients will respond to therapy, and provide a durable response.

1.2 Rationale for QNEXA Therapy

QNEXA is an orally administered, once-daily weight loss therapy that contains a combination of immediate-release phentermine hydrochloride (PHEN) and extended-release topiramate (TPM). These two agents suppress appetite through complementary and distinct mechanisms (decreased hunger and increased satiety), leading to additive effects on weight loss. Both PHEN and TPM are U.S.-marketed drugs approved at higher doses than those contained in QNEXA.

Phentermine, a synthetic sympathomimetic amine, is an anorectic agent approved by the FDA for over 52 years at a recommended dose of 37.5 mg/day as a short-term adjunct to a weight-loss regimen based on exercise, behavior modification, and caloric restriction. Phentermine is the most commonly used anti-obesity drug in the U.S., with approximately 6.5 million prescriptions written in 2011 (IMS data). The primary mechanism of action appears to be pharmacologically induced anorectic effect via release of norepinephrine in the hypothalamus. Studies suggest that increased circulating catecholamines may cause appetite suppression by increasing blood leptin concentrations; other studies have demonstrated a correlation between serum leptin concentrations and body weight (Heymsfield 1999; Montague 1997).

Topiramate, a sulfamate-substituted monosaccharide, is a neurotherapeutic agent first approved in 1996 for treatment of epilepsy at recommended doses of 200-400 mg/day and later approved in 2004 for migraine prophylaxis at a recommended dose of 100 mg/day. The most recent FDA approval, for use in patients down to 2 years of age was in July 2011. More than 10 million prescriptions were written for topiramate in 2011 (IMS data). The majority of topiramate use is in migraine prevention. Topiramate has multiple confirmed molecular mechanisms that can mediate the pharmacodynamic effects leading to weight loss. Consistent with these mechanisms, several published clinical studies have shown that topiramate monotherapy produces significant weight loss in obese individuals and clinically meaningful improvements in lipid parameters, glycemic control, and blood pressure (Ben-Menachem 2003 ; Bray 2003; Wilding 2004; Tonstad 2005; Stenlöf 2007). Available pharmacological evidence suggests that topiramate-induced weight loss may result from increased satiety, increased taste aversion, increased energy expenditure, and decreased caloric intake (Bray 2003; Richard 2000

; Richard 2002; Picard 2000; Supuran 2008). Topiramate, however, is associated with dose-limiting side effects, including paresthesia, dizziness, somnolence, insomnia, depression, and difficulty with memory and concentration, which prevent or limit its use as a single agent at the doses necessary to produce significant weight loss or cardiometabolic benefits.

VIVUS developed QNEXA based on the hypothesis that use of lower than currently approved doses of the individual agents comprising QNEXA, in conjunction with complementary mechanisms and oppositional pharmacodynamic effects, may provide a safe and effective pharmacotherapy for achieving and maintaining weight loss and for treating obesity-related comorbidities in overweight and obese adults.

QNEXA is comprised of an immediate-release formulation of phentermine hydrochloride and an extended-release formulation of topiramate in a single capsule. Peak exposure to each drug is separated by 7 to 8 hours so that phentermine peak exposure occurs in the morning and topiramate peak exposure occurs near late afternoon/evening. The quantitative composition is indicated as milligrams by weight of phentermine (free base) and topiramate. Proposed dosage strengths are 15 mg/92 mg (Top dose), 7.5 mg/46 mg (Mid dose), and 3.75mg/23 mg (Low dose). Mid dose QNEXA is the recommended treatment dose. Top dose QNEXA is intended for subjects who, while responsive to Mid dose QNEXA, have not achieved their weight loss goals or improvements in obesity-related comorbidities. Low dose QNEXA may be considered as a treatment dose in subjects based on individual treatment goals and/or ability to tolerate Mid dose QNEXA.

1.3 Proposed Indication

QNEXA is indicated for the treatment of adult obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with diet and exercise. QNEXA is recommended for obese patients (BMI ≥30 kg/m^2) or overweight patients (BMI ≥27 kg/m^2) with obesity-related comorbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

As per FDA's request, QNEXA will be contraindicated in women who are pregnant, and that the contraindication will state that if a woman becomes pregnant while taking QNEXA, treatment should be discontinued immediately.

1.4 Dosage and Administration

The respective doses of the QNEXA components were originally chosen based on documented weight loss and tolerability in published studies of the individual agents (Bray 1998; Bray 1999; Bray 2003) and confirmed in the early QNEXA clinical trial program. The results of a Phase 2 proof-of-concept study established the ceiling target dose and target ratio and demonstrated that the phentermine/topiramate combination produced a magnitude of weight loss (~10%) that exceeded current pharmacotherapies, exceeded either drug as monotherapy, and exceeded FDA criteria for approval of weight-loss agents.

Proposed QNEXA labeling recommends initiating therapy with QNEXA Low dose for 14 days, taken once daily (in the morning) with or without food, and then increasing to the Mid

dose for 90 days. After 90 days, if weight loss is <3%, treatment should be discontinued. If weight loss is ≥3%, then the Mid dose should be continued for another 90 days. If weight loss goals are not achieved at day 180, the patient may be titrated to the Top dose based on tolerability.

In patients with moderate renal impairment (creatinine clearance [Cr_{cl}] ≥30 to <50 mL/min) and severe renal impairment (Cr_{cl}<30 mL/min), the maximum dose should not exceed 7.5 mg/46 mg (Mid dose).

Low dose QNEXA may be considered as a treatment dose in subjects based on individual treatment goals and/or ability to tolerate Mid dose QNEXA.

1.5 Regulatory History

Important aspects of the QNEXA development program, including the number of subjects treated, the populations evaluated, the duration and design of the studies providing pivotal efficacy and safety data, statistical consideration, and the endpoints evaluated in these studies were agreed upon by VIVUS and the FDA through a Special Protocol Assessment. An independent Data Safety Monitoring Board oversaw all studies in the Phase 3 program.

The original New Drug Application (NDA) for QNEXA was submitted to FDA on December 28, 2009. The NDA included results of a comprehensive clinical development program conducted by VIVUS specific to the efficacy and safety of QNEXA for the treatment of obesity. Because the active components, phentermine hydrochloride and topiramate, are FDA-approved products for chronic conditions at doses at least as high as those proposed in QNEXA, the NDA also relied in part on the FDA's previous determination of safety for these products.

The original NDA was reviewed at a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on July 15, 2010. The Committee voted 10 to 6 against the approval of QNEXA based primarily on concerns regarding potential safety issues associated with the individual components, including increased heart rate, teratogenicity and suicidality. On October 28, 2010, FDA issued a complete response letter (CRL) for QNEXA requesting a comprehensive assessment of topiramate's and QNEXA's teratogenic potential including a detailed plan and strategy to evaluate and mitigate any potential teratogenic risks in women of child bearing potential (WOCBP), evidence that QNEXA-associated elevations in heart rate (mean 1.6 beats per minute [bpm] on the Top dose) do not increase the risk for major adverse cardiovascular events, and the results from a recently-completed 52-week extension study (study OB-305) for a subset of patients who had completed study OB-303, one of the 1-year pivotal trials. Concerns regarding suicidality risk were not raised in FDA's letter and were, therefore, presumably adequately addressed in the original NDA, which includes proposed labeling with the same suicidality information found in the topiramate label. In addition, no efficacy deficiencies were noted and VIVUS understands that the Phase 3 program results have been deemed sufficient to establish the efficacy of QNEXA in treating obesity.

With FDA's agreement, on October 17, 2011, VIVUS resubmitted the NDA for approval with a contraindication for use in WOCBP. FDA accepted the filing but after further discussion

with the agency, FDA has asked and VIVUS agreed to remove the contraindication for WOCBP because a contraindication typically indicates that a drug should not be used in that population because of the risk of use clearly outweighs any possible therapeutic benefit. In addition, FDA asked that VIVUS include elements in its REMS program that focus on patient and physician educational. VIVUS amended its risk management plan to focus on a robust educational and safe use effort designed to minimize the risk of fetal exposure to QNEXA. The discussion in this briefing document presents only the latter approach. VIVUS would be pleased to discuss the contraindication approach at the EMDAC, if requested.

Because the QNEXA nonclinical and clinical programs were presented to the EMDAC in July 2010, the discussion in this briefing document provides a brief overview of the Phase 3 efficacy and safety program and then focuses primarily on issues raised by FDA in the CRL. A tabular overview of the entire clinical program, baseline and demographic tables for the Phase 3 studies, a reprint of the journal publication for the two-year extension study, a protocol synopsis for a planned Phase 4 QNEXA cardiovascular outcomes trial, case reports of all MACE events, a summary of psychiatric and cognitive safety data, an overview of nonclinical teratology studies, as well as overviews of biopharmaceutics and clinical pharmacology data are located in the appendices for completeness.

2 CLINICAL DEVELOPMENT AND DEMONSTRATION OF EFFICACY

2.1 Clinical Development Program

The initial QNEXA clinical development program included three Phase 3 studies: study OB-301, a 28-week study confirming efficacy of QNEXA over PHEN and TPM alone; and studies OB-302 and OB-303, both 56-week pivotal trials that together evaluated the efficacy and safety of three fixed-dose combinations of QNEXA for the treatment of adult obesity in individuals with and without obesity-related comorbidities. These studies were presented in detail at the 2010 EMDAC. Study OB-305, a 1-year extension of study OB-303, was recently completed and therefore not included in the original NDA or the prior EMDAC meeting.

The QNEXA clinical development program also included five Phase 2 studies (OB-201, OB-202, OB-204, DM-230, DM-231). Studies OB-201 and OB-202 were proof-of-concept studies in overweight and obese subjects without and with type 2 diabetes, respectively, that compared the effects of QNEXA versus monotherapy with phentermine or topiramate, or placebo. Studies DM-230 and DM-231 were consecutive extensions to the OB-202 study. OB-204 (which was not part of the original submission but was included in the resubmission) evaluated the use of QNEXA in severe obstructive sleep apnea in obese subjects. In addition, the data from ten Phase 1 studies were provided as part of the overall safety database. Full clinical program summary tables can be found in **Appendix 1**.

Table 1 summarizes the duration and extent of population exposure throughout the clinical development program.

Table 1. Extent of Exposure for the QNEXA Clinical Development Program

	Number of Subjects by Treatment Group					
	QNEXA Low	QNEXA Mid	QNEXA Top	QNEXA Other	QNEXA (All Doses)	Placebo
Number of subjects dosed	366	712	2,017	195	3,165	1,893
Number of subjects with ≥6 months of exposure	168	467	1,328	--	1,963	1,206
Number of subjects with ≥12 months of exposure	143	349	1,034	--	1,526	869
Number of subjects with ≥24 months of exposure	--	128	246	--	374	197

QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.2 Key Efficacy Findings

Key efficacy findings from the QNEXA clinical development program include:

- Subjects treated with each of the three doses of QNEXA experienced significantly greater percentage and categorical weight loss from baseline compared with subjects treated with placebo. Weight loss from baseline observed at Week 56 was sustained through Week 108.

- Subjects treated with QNEXA Mid dose and Top dose experienced greater percentage and categorical weight loss from baseline compared with subjects treated with the individual (phentermine or topiramate) components alone or placebo.

- Clinically-meaningful dose-related improvements in obesity-related comorbidities, such as blood pressure, blood lipids, and diabetes markers, were observed across all QNEXA treated groups; improvements of the greatest magnitude were observed in pivotal study OB-303, which included overweight and obese subjects who had ≥2 comorbidities at baseline.

- QNEXA-treated subjects had greater reductions of concomitant medications to treat obesity-related comorbidities compared with placebo subjects.

2.3 Phase 2 Clinical Trials

The QNEXA clinical development program included five Phase 2 studies (OB-201, OB-202, OB-204, DM-230, and DM-231), which provide supporting data regarding QNEXA's safety and efficacy in the treatment of obesity. Study OB-201 was a proof-of-concept factorial design study in obese subjects to evaluate the safety and effectiveness of QNEXA compared to its single agent phentermine and topiramate components. Study OB-202 was a proof-of-concept, randomized, placebo-controlled study in overweight and obese subjects with type 2 diabetes. Studies DM-230 and DM-231 were consecutive extensions of study OB-202. Study

OB-204 was a randomized, placebo-controlled study evaluated the use of ONEXA in overweight or obese subjects with severe obstructive sleep apnea.

Of the five Phase 2 QNEXA studies conducted, three provide efficacy information unique to the Phase 2 program based on differences in Phase 2 and Phase 3 study designs. These three studies are briefly discussed below.

2.3.1 Study OB-202: Proof-of-Concept Study in Obese Subjects with Type 2 Diabetes

Study OB-202 was a randomized, double-blind, placebo-controlled study in overweight and obese adults <70 years of age with a BMI >27 kg/m^2 and <45 kg/m^2 with type 2 diabetes (HbA_{1c} >7.0% and <12.0%) controlled by diet or oral antidiabetic medication, which compared phentermine (15 mg) and topiramate (100 mg) combination therapy with placebo after 28 weeks of treatment.

The primary endpoint was change from baseline in HbA_{1c} at week 28 using ITT-LOCF. Analysis of Covariance (ANCOVA) was used to compare the two treatment groups. Key secondary endpoints were changes in cardiovascular/metabolic risk factor medication, changes in lipid parameters, changes in blood pressure, changes in other glycemic indices, percent and categorical weight loss, changes in waist circumference, and changes in BMI. Continuous secondary endpoints were analyzed using ANCOVA or nonparametric methods. Binary secondary endpoints were analyzed using logistic regression. No adjustments were made for multiple comparisons.

In total, 210 subjects were randomly assigned to treatment. Of the 210 subjects, 165 (79%) subjects completed the study and 45 (21%) subjects discontinued from the study. At baseline, mean weight was 96.4 kg, mean BMI was 35.2 kg/m^2, mean waist circumference was 109.9 cm, and mean HbA_{1c} was 8.7%.

Treatment with phentermine 15 mg/topiramate 100 mg resulted in a 1.1% decrease in HbA_{1c} at Week 28 with LOCF compared to placebo, which resulted in a 0.6% decrease (p=0.0007). The treatment comparisons between phentermine 15 mg/topiramate 100 mg and placebo were also significant for changes in fasting blood glucose and insulin sensitivity indices at Week 28. Treatment with phentermine 15 mg/topiramate 100 mg resulted in a significantly greater percent weight loss and a higher proportion of subjects with ≥5% and ≥10% weight loss than placebo at Week 28 with LOCF. Treatment with phentermine 15 mg/topiramate 100 mg also resulted in significant decreases in waist circumference, SBP, DBP, and TG at Week 28 with LOCF relative to placebo.

2.3.2 Study DM-230: 6-month Extension of OB-202 Study in Obese Subjects with Type 2 Diabetes

Study DM-230 was a 28-week extension of study OB-202 evaluating the long-term safety and efficacy of QNEXA in overweight and obese adults with type 2 diabetes. Subjects who completed study OB-202 and opted to participate in this extension study remained on the double-blind treatment to which they had been randomized in study OB-202. During the extension study, subjects in the active treatment group received QNEXA Top dose capsules

instead of the phentermine 15 mg capsules and topiramate 100 mg capsules administered separately in study OB-202.

The primary endpoint was change from Study OB-202 baseline in HbA_{1c} at Week 56 using ITT-LOCF. ANCOVA was used to analyze the two treatment groups. Key secondary endpoints were change in HbA_{1c} levels at Week 44, proportions of subjects achieving HbA_{1c} levels at or below 7% and 6.5%, changes in other glycemic indicators, changes in lipid parameters, blood pressure, and changes in cardiovascular/metabolic risk factor medications. Additional endpoints included differences in absolute and percent weight loss, waist circumference, and BMI. Secondary endpoints were analyzed using ANCOVA or nonparametric measures as appropriate, while percentages of subjects achieving 7% or 6.5% HbA_{1c} levels were analyzed using logistic regression. No adjustments were made for multiple comparisons.

Of the 210 subjects enrolled in study OB-202, 130 (61.9%) subjects enrolled into study DM-230. Of these, 120 (92.3%) subjects completed the study, and 10 (7.7%) discontinued from the study. At study OB-202 baseline, mean weight was 96.3 kg, mean BMI was 35.3 kg/m^2, mean waist circumference was 109.8 cm and mean HbA_{1c} was 8.7% for the study DM-230 population.

Treatment with QNEXA Top dose resulted in a 1.6% reduction in HbA_{1c} levels at Week 56 with LOCF compared to placebo, which resulted in a 1.2% reduction in HbA_{1c} (p=0.0381). The treatment comparisons between QNEXA Top dose and placebo groups were also significant for SBP, fasting glucose, fasting insulin, percent weight loss, waist circumference and BMI at Week 56. There was a significantly greater net increase in use of antidiabetic medication in the placebo group compared to the QNEXA group.

2.3.3 Study OB-204: Study in Obese Subjects with Severe Obstructive Sleep Apnea

Study OB-204 was a randomized, double-blind, placebo-controlled study in obese adults 30-65 years of age with a BMI $\geq$30 kg/m^2 and $\leq$40 kg/m^2 with obstructive sleep apnea hypopnea syndrome (OSA), which compared QNEXA Top dose with placebo over 28 weeks of treatment.

The primary efficacy endpoint was the change in apnea/hypoxia index (AHI) between baseline and Week 8 and Week 28 or ET using LOCF. ANCOVA with treatment groups as the main effect and baseline body weight as the covariate was used to compare the treatment groups. Key secondary endpoints were changes in respiratory disturbance index (RDI), changes in various sleep quality measures, changes in oxygen saturation indices, percent and categorical weight loss, changes in blood pressure, and changes in lipid profiles. Continuous secondary endpoints were analyzed using ANCOVA. Categorical variables were evaluated by logistic regression. No adjustments were made for multiple comparisons.

A total of 45 subjects were randomly assigned to treatment. Of the 45 subjects, 40 (88.9%) completed the study and 5 (11.1%) discontinued from the study. At baseline, mean weight was 105.3 kg, mean BMI was 35.6 kg/m^2, and mean AHI was 43.5 in the placebo group and 45.5 in the QNEXA Top dose group.

QNEXA Top dose demonstrated significant reductions from baseline in AHI events at Week 8 (p=0.0009) and Week 28 (p=0.0084) compared with placebo. At Week 28, the number of apnea/hypopnea events was reduced from a mean of 46 to a mean of 13 events per hour of sleep in the QNEXA treatment group, as compared to a reduction from 45 to 27 events per hour of sleep in the placebo group. Significant improvements were also seen in the QNEXA group over the placebo group in RDI, sleep quality measures and oxygen saturation. Consistent with other Phase 2 studies, treatment comparisons between QNEXA Top dose and placebo groups were also significant for percent and categorical weight loss, SBP and HDL-C.

2.4 Phase 3 Trial Descriptions and Study Populations

The three Phase 3 studies in the QNEXA pivotal clinical development program included a 28-week factorial study conducted to confirm the contribution of each component (PHEN and TPM) to the weight loss effects of QNEXA (OB-301), and two 1-year studies to evaluate weight loss effects of QNEXA in morbidly obese subjects (OB-302) and subjects with two or more obesity-related comorbidities (OB-303). Studies OB-301 and OB-303 were designed in consultation with FDA under a Special Protocol Assessment (SPA). Studies OB-302 and OB-303 meet the standards set forth in the Agency's current Guidance for Industry: "Developing Products for Weight Management" (FDA Guidance 2007). In accordance with the FDA Obesity Guidance, weight loss data from the Phase 3 studies are presented for a modified intent-to-treat (referred to herein as ITT for simplicity) set, defined as all randomized subjects who provided a baseline measurement of body weight, received at least one dose of study drug, and had at least one post-dose assessment of body weight. Data are presented at Week 56 or End of Treatment with last observation carried forward (ITT-LOCF). Sensitivity analyses employing other imputation strategies, including baseline observation carried forward and mixed-model imputation methods were also used to assess the effect of high rate of dropouts expected in obesity trials on the results, consistent with the FDA Guidance, and demonstrated results consistent with the LOCF analysis. Throughout the Phase 3 program, subjects were counseled to participate in the LEARN® Program for Weight Management, a 16-week program that incorporates tools to facilitate lifestyle, attitude, relationship, nutrition, and exercise changes.

As mentioned above, due to the previous finding that the 1-year pivotal studies demonstrate the efficacy of QNEXA, each of the three Phase 3 studies is discussed only in brief below, with the majority of this briefing book dedicated to the results of the 2-year extension study and the safety concerns raised in the CRL.

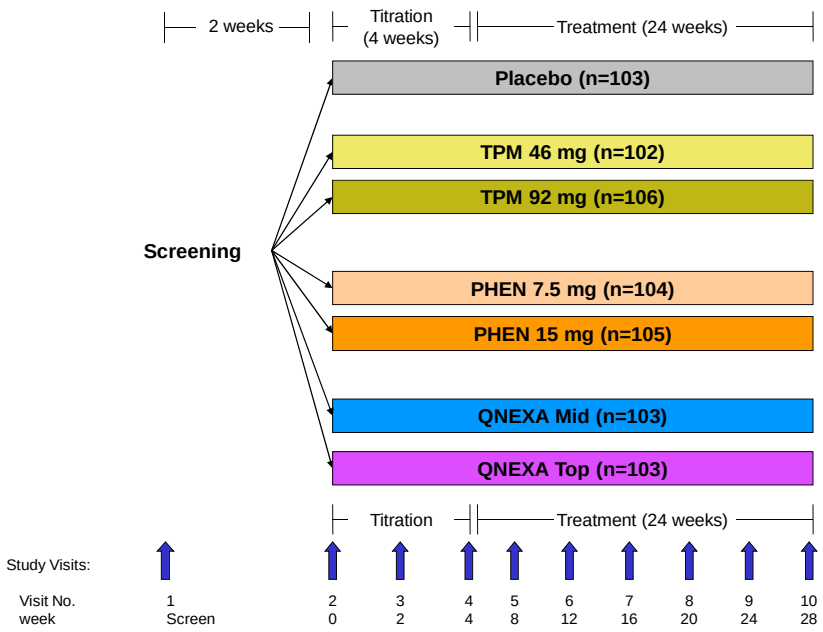
2.4.1 OB-301: Six-Month Factorial Study

OB-301, a randomized, double-blind, placebo-controlled, six-month multicenter factorial (seven-arm) trial in obese adults ≤70 years of age with a BMI ≥30 and ≤45 kg/m^2, compared weight loss from baseline in subjects treated with placebo, QNEXA Mid dose, or QNEXA Top dose, and the respective single-agent phentermine and extended-release topiramate components at doses corresponding to both the Mid dose and Top dose combinations, after 28 weeks of treatment. The study schema is diagrammed in **Figure 4**.

The co-primary efficacy endpoints were percent weight loss at Week 28 and percentage of subjects with at least 5% weight loss at Week 28 in the ITT population using LOCF for missing data. Each of three pairwise comparisons (QNEXA dose versus each single agent comprising the combination and the QNEXA dose versus placebo) was required to reach the 5% significance level for either co-primary endpoint in order for efficacy of that dose to be declared. A step-down multiple testing procedure, testing the QNEXA Top dose first, was used to control the overall type I error. Comparisons between treatments for percent weight loss were assessed using a two-way ANCOVA model with factors of treatment and gender and with baseline weight as the covariate. Comparisons between treatments for categorical weight loss were evaluated by logistic regression.

Secondary endpoints included proportion of subjects achieving ≥10% weight loss, change from baseline in waist circumference, and change from baseline in IWQOL composite and individual domain scores at Week 28. Secondary endpoints based on continuous data were evaluated in a manner similar to the primary endpoint. Categorical variables were evaluated by logistic regression. A step-down strategy analogous to that used for the primary endpoint was used to protect overall alpha levels for these comparisons. Clinical laboratory information was captured as a safety endpoint.

Figure 4. OB-301 Study Schematic



PHEN = phentermine HCl; QNEXA = fixed-dose combination of phentermine and extended-release topiramate; TPM = extended-release topiramate.
QNEXA Mid, 7.5mg/46 mg; QNEXA Top, 15mg/92 mg.

2.4.1.1 OB-301 Study Population

Most subjects were female (79.2%) and Caucasian (79.2%). The mean age of subjects was 45.6 years. At baseline, mean weight was 101.3 kg, mean BMI was 36.3 kg/m^2, mean waist

circumference was 111.1 cm, mean systolic blood pressure (SBP) was 122.1 mmHg and mean diastolic blood pressure (DBP) was 79.0 mmHg. With the exception of race, the treatment groups were comparable with respect to demographic and baseline characteristics including mean weight, BMI, and waist circumference at baseline.

A total of 756 eligible subjects were randomly assigned to receive daily treatment with placebo (n=109), phentermine 7.5 mg (n=109), phentermine 15 mg (n=108), extended-release topiramate 46 mg (n=108), extended-release topiramate 92 mg (n=107), QNEXA Mid dose (n=107), or QNEXA Top dose (n=108). Randomization was stratified by sex to ensure a similar distribution of male and female subjects across the treatment groups.

For efficacy results see **Section 2.5**.

2.4.2 OB-302: Pivotal Study in Severely Obese Subjects

Study OB-302, a randomized, double-blind, placebo-controlled, multicenter trial in severely obese adult subjects ≤70 years of age with a BMI ≥35 kg/m^2 (no upper limit), compared weight loss from baseline in subjects treated with placebo, QNEXA Low dose, or QNEXA Top dose in a 2:1:2 randomization after 56 weeks of treatment. Subjects with type 2 diabetes, hypertension (blood pressure >140/90 mmHg or treatment with >2 antihypertensive medications), and hypertriglyceridemia (triglycerides [TG] >200 mg/dL or treatment with ≥2 lipid-lowering medications) were excluded from participation in this study. The study schema is diagrammed in **Figure 5**.

The co-primary endpoints were the differences between QNEXA and placebo groups in mean percent weight loss from baseline at Week 56, and the percent of subjects with weight loss of 5% or more at Week 56 in the ITT population using LOCF for missing data. Comparisons between treatments of percent weight loss were assessed using ANCOVA with factors of treatment and gender with baseline weight as the covariate. A step-down multiple comparison procedure, starting with QNEXA Top dose, was used to compare each dose group with placebo.

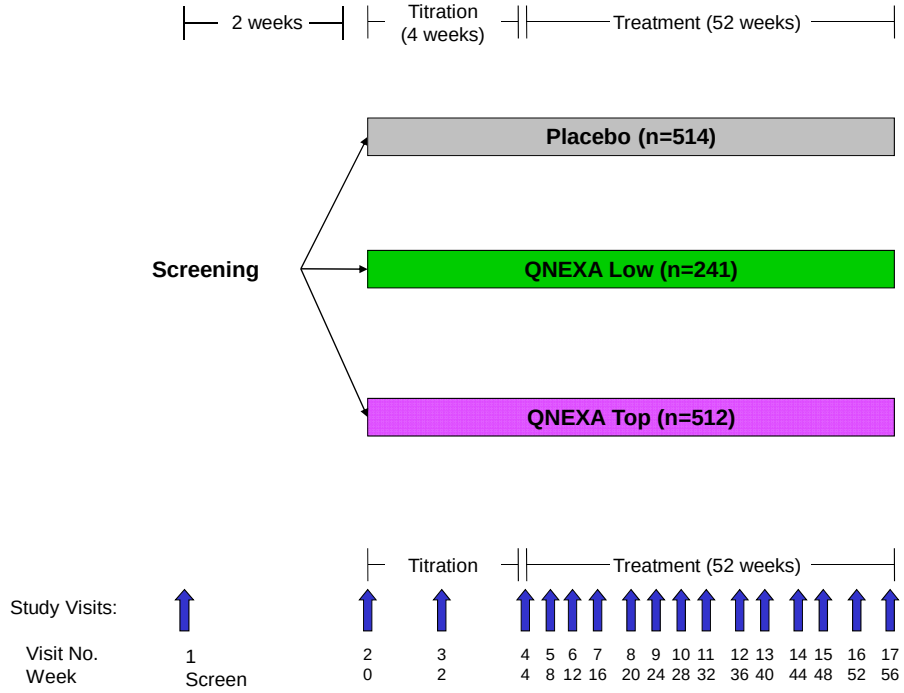
Secondary efficacy endpoints were:

- The difference in absolute weight loss between baseline and Week 56 between QNEXA and placebo groups;
- The difference in percent of subjects with weight loss of 10% or more at Week 56 between QNEXA and placebo groups; and
- The difference in change in waist circumference from baseline to Week 56 between QNEXA and placebo groups.

A step-down strategy was implemented to protect the overall alpha. Differences in absolute weight reduction and change in waist circumference were compared using the same ANCOVA model used for the primary endpoint. Categorical weight loss was assessed using logistic regression.

Additional efficacy endpoints included effects on IWQOL-Lite, body composition, obesity-associated risk factors (TC, TG, LDL-C, HDL-C, fasting glucose and blood pressure) and change from baseline in BMI.

Figure 5. OB-302 Study Schematic



QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Top, 15 mg/92 mg.

2.4.2.1 OB-302 Study Population

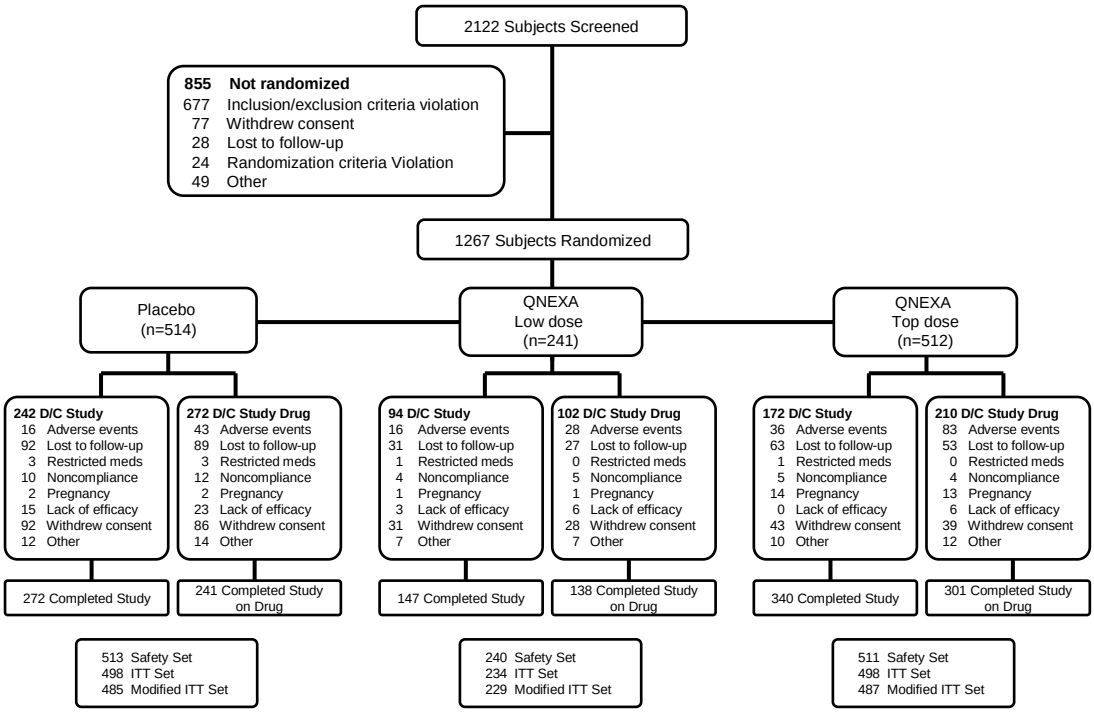
Most subjects were female (82.9%) and Caucasian (80.0%). The mean age of subjects was 42.6 years. At baseline, mean weight was 116.1 kg, mean BMI was 42.1 kg/m^2, mean waist circumference was 120.5 cm, mean SBP was 122.0 mmHg and mean DBP was 77.4 mmHg. The treatment groups were comparable with respect to demographic and baseline characteristics, including mean weight, BMI, waist circumference, blood pressure, lipids, and fasting serum glucose. Randomization was stratified by sex to ensure a similar distribution of male and female subjects across the treatment groups. **Appendix 2** provides a summary of demographic and baseline characteristics of subjects enrolled in study OB-302.

A total of 1,267 subjects were assigned randomly to treatment **(Figure 6)**. In total, 759 (59.9%) subjects completed all study visits, and 508 (40.1%) subjects discontinued from the study. The percentages of subjects who completed the study were 52.9% in the placebo group, 61.0% in the QNEXA Low dose group, and 66.4% in the QNEXA Top dose group. Of the 1,267 randomized subjects, 680 (53.7%) subjects completed all study visits on study drug, and 584 (46.1%) subjects discontinued study drug. The percentages of subjects who completed the study on study drug were 46.9% in the placebo group, 57.3% in the QNEXA Low dose group,

and 58.8% in the QNEXA Top dose group. A total of 79 subjects who discontinued study drug completed follow-up visits.

For efficacy results see **Section 2.5**.

Figure 6. Subject Disposition – Study OB-302



Subjects may be counted in both discontinuation sections.
D/C = discontinued; ITT = intent-to-treat; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23mg; QNEXA Top, 15 mg/92 mg.

2.4.3 OB-303: Pivotal Study in Overweight and Obese Subjects with Comorbidities

Study OB-303 was a randomized, double-blind, placebo-controlled, multicenter trial, of weight loss from baseline at 56 weeks in adult subjects ≤70 years of age with a BMI ≥27 and ≤45 kg/m^2 with ≥2 of the following obesity-related comorbid conditions: elevated blood pressure or requirement for ≥2 antihypertensive medications, elevated TG or requirement for ≥2 lipid-lowering medications, elevated fasting blood glucose or diabetes, and/or waist circumference ≥102 cm for men or ≥88 cm for women. Subjects with diabetes did not have a lower limit on the BMI inclusion criterion. Eligible subjects were randomly assigned 2:1:2 to receive daily treatment with placebo, QNEXA Mid dose, or QNEXA Top dose. The study schema is diagrammed in **Figure 7**.

The co-primary endpoints were the differences between QNEXA and placebo groups in mean percent weight loss from baseline at Week 56, and the percent of subjects with weight loss of 5% or more at Week 56 in the ITT population using LOCF for missing data. Comparisons between treatments of percent weight loss were assessed using ANCOVA with factors of

treatment, gender and diabetic status with baseline weight as the covariate. A step-down multiple comparison procedure, starting with QNEXA Top dose, was used to compare each dose group with placebo.

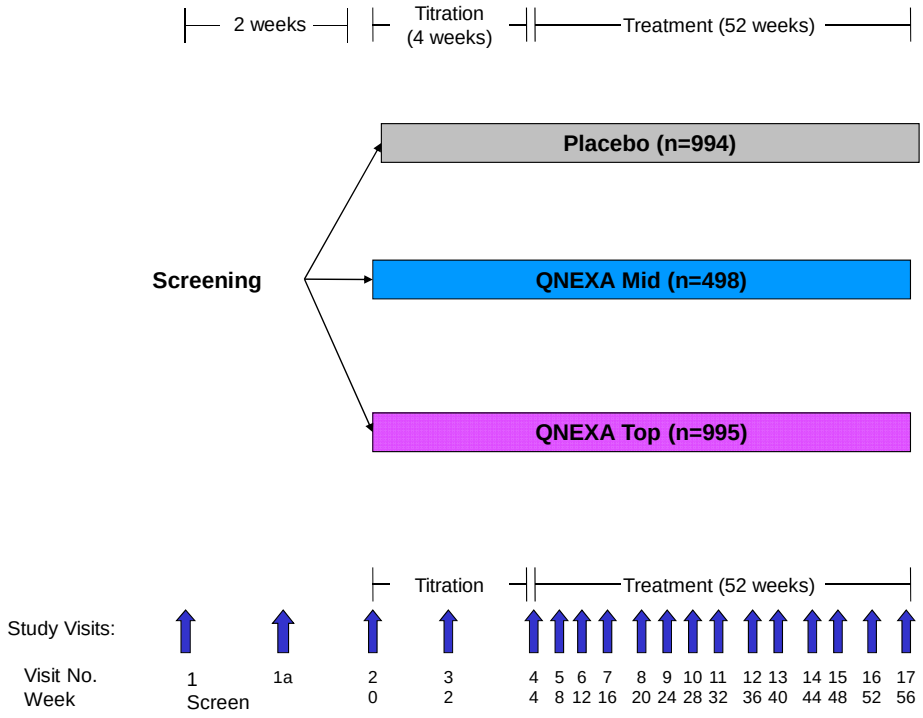
Secondary efficacy endpoints were:

- The difference in absolute weight loss between baseline and Week 56 between QNEXA and placebo groups;
- The difference in percent of subjects with weight loss of 10% or more at Week 56 between QNEXA and placebo groups; and
- The difference in change in waist circumference from baseline to Week 56 between QNEXA and placebo groups.

A step-down strategy, analogous to that used for the primary endpoint was implemented to protect the overall alpha. Differences in absolute weight reduction and change in waist circumference were compared using the same ANCOVA model used for the primary endpoint. Categorical weight loss was assessed using logistic regression.

Additional efficacy endpoints included effects on IWQOL-Lite, body composition, obesity-associated risk factors (TC, TG, LDL-C, HDL-C, fasting glucose and blood pressure) and change from baseline in BMI.

Figure 7. OB-303 Study Schematic



QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

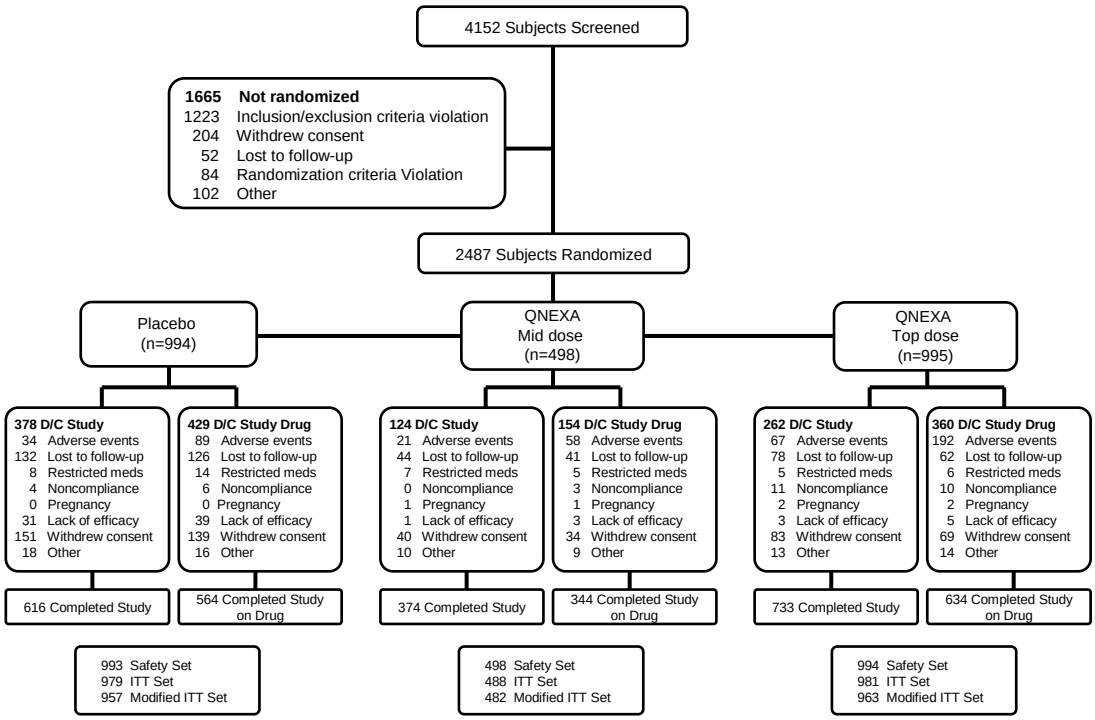
2.4.3.1 OB-303 Study Population

Most subjects were female (69.8%) and Caucasian (86.0%). The mean age of subjects was 51.1 years. At baseline, mean weight was 103.1 kg, mean BMI was 36.6 kg/m^2, mean waist circumference was 113.2 cm, mean SBP was 128.4 mmHg and mean DBP was 80.6 mmHg. At baseline, mean low-density lipoprotein cholesterol (LDL-C) was 123.1 mg/dL, mean high-density lipoprotein cholesterol (HDL-C) was 48.9 mg/dL, mean total cholesterol (TC) was 204.5 mg/dL, mean TG was 162.5 mg/dL, mean hemoglobin A_{1c} (HbA_{1c}) was 5.9% and mean fasting serum glucose was 106.1 mg/dL. The treatment groups were comparable with respect to demographic and baseline characteristics, including mean weight, BMI, waist circumference, blood pressure, lipids, HbA_{1c}, and fasting serum glucose. Subjects with obesity-related comorbidities were balanced across treatment groups. **Appendix 2** provides a summary of demographic and baseline characteristics of subjects enrolled in study OB-303.

A total of 2,487 subjects were assigned randomly to treatment **(Figure 8)**. In total, 1,723 (69.3%) subjects completed all study visits, and 764 (30.7%) subjects discontinued from the study. The percentages of subjects who completed the study were 62.0% in the placebo group, 75.1% in the QNEXA Mid dose group, and 73.7% in the QNEXA Top dose group. Of the 2,487 randomized subjects, 1,542 (62.0%) subjects completed all study visits on study drug. The percentages of subjects who completed the study on study drug by treatment were 56.7% in the placebo group, 69.1% in the QNEXA Mid dose group, and 63.7% in the QNEXA Top dose group. In total, 181 subjects completed study visits off study drug.

For efficacy results see **Section 2.5**.

Figure 8. Subject Disposition – Study OB-303



Subjects may be counted in both discontinuation sections.
D/C = discontinued; ITT = intent-to-treat; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid dose, 7.5 mg/46 mg; QNEXA Top dose, 15 mg/92 mg.

2.5 Results and Integrated Efficacy Summary

Results across all three QNEXA Phase 3 trials were consistent with regard to weight loss. Treatment with QNEXA, at all dose levels tested, resulted in statistically significant dose-dependent weight loss from baseline compared with placebo. The magnitude and time course of weight loss was comparable across trials. The proportions of subjects achieving defined categories of weight loss were higher among the QNEXA groups compared with placebo. Results from the categorical analysis of weight loss were consistent with those from the analysis of percent weight loss across all of the studies. The observed weight loss in the two pivotal 1-year trials exceeded FDA guidance for weight management products, with no rebound weight gain observed during the trial period.

Presented in this section are the efficacy results for the pivotal Phase 3 program. All three studies utilized mean percent weight loss and categorical weight loss as co-primary endpoints. Secondary and exploratory endpoints were not uniform across all three studies, and are thus presented in order of interest using nominal p-values as appropriate.

2.5.1 Primary Endpoints and Other Measures of Weight Loss at One Year

2.5.1.1 Percent Weight Loss

Table 2 presents the results for percent weight loss at study endpoint for each of the individual Phase 3 studies. This was a co-primary endpoint in each study. Results were consistent across all of the studies in demonstrating statistically significant, dose-related, and clinically meaningful percent weight loss with QNEXA when compared with placebo.

Table 2. Percent Weight Loss at Study Endpoint – Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)

	OB-301			OB-302			OB-303		
	Percent Weight Loss at Week 28[a]			Percent Weight Loss at Week 56[a]			Percent Weight Loss at Week 56[a]		
Treatment	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value	n	LS Mean (SE)	p-value
Placebo	103	1.7 (0.61)	--	498	1.6 (0.40)	--	979	1.2 (0.28)	--
QNEXA Low	--	--	--	234	5.1 (0.54)	<0.0001	--	--	--
QNEXA Mid	103	8.5 (0.62)	<0.0001	--	--	--	488	7.8 (0.37)	<0.0001
QNEXA Top	103	9.2 (0.61)	<0.0001	498	10.9 (0.39)	<0.0001	981	9.8 (0.28)	<0.0001
PHEN 7.5 mg	104	5.5 (0.61)	0.0003[b]	--	--	--	--	--	--
PHEN 15 mg	106	6.1 (0.61)	0.0001[c]	--	--	--	--	--	--
TPM 46 mg	102	5.1 (0.61)	<0.0001[b]	--	--	--	--	--	--
TPM 92 mg	105	6.4 (0.62)	0.0009[c]	--	--	--	--	--	--

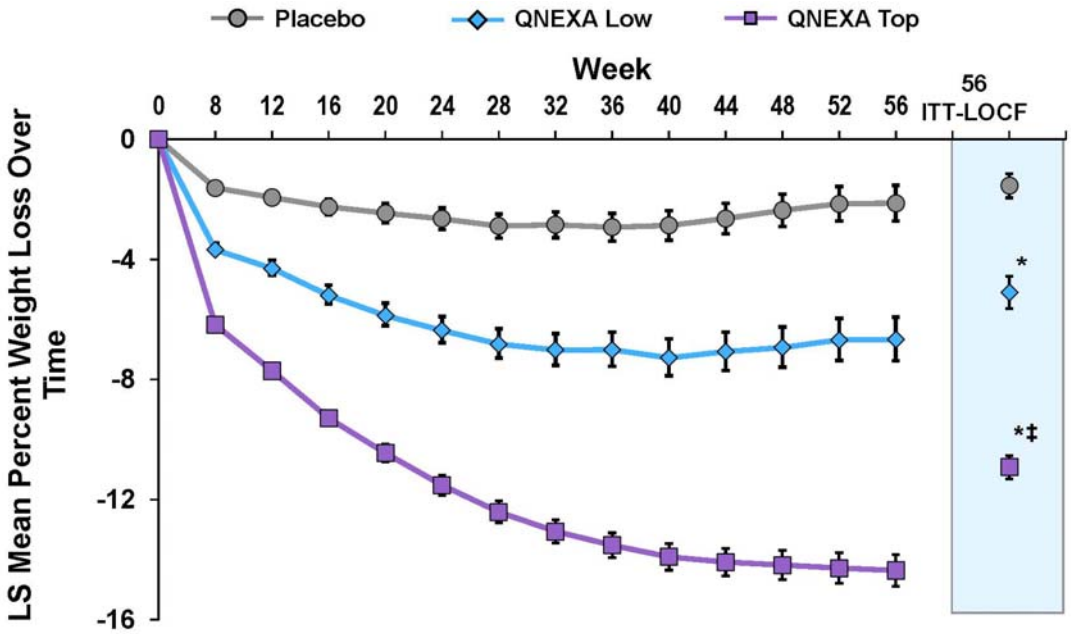
a. LS mean, SE, and two-sided p-value are from ANCOVA model with treatment and gender as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA to placebo.
b. p-value versus QNEXA Mid.
c. p-value versus QNEXA Top.
ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; PHEN = phentermine;
QNEXA = fixed-dose combination of phentermine and topiramate; SE = standard error; TPM = topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In study OB-301, a 6-month factorial study, treatment with QNEXA resulted in a significantly greater LS mean percent weight loss from baseline at Week 28 compared with placebo. Study OB-301 also demonstrated the contribution of both phentermine and topiramate to the weight loss benefit of QNEXA.

In studies OB-302 and OB-303, 1-year studies in obese subjects with and without comorbidities, treatment with QNEXA Top dose resulted in weight loss that occurred rapidly and continued progressively through Week 56, at which time, subjects who had completed study OB-302 on drug lost 14.4% of baseline body weight, and subjects who had completed study OB-303 on drug lost 12.4% of baseline body weight. For the QNEXA Low dose and Mid dose groups, mean percent weight loss progressively increased from baseline to Week 40 and then was relatively stable from Week 40 to the end of the study. Week 56 weight loss for subjects completing study on drug was 6.7% for QNEXA Low dose (OB-302) and 9.6% for QNEXA Mid dose (OB-303). For the placebo groups, mean percent weight loss was relatively stable from Week 28 to the end of the study, with the Week 56 mean percent weight loss averaging 2.1% in OB-302 and 1.6% in OB-303.

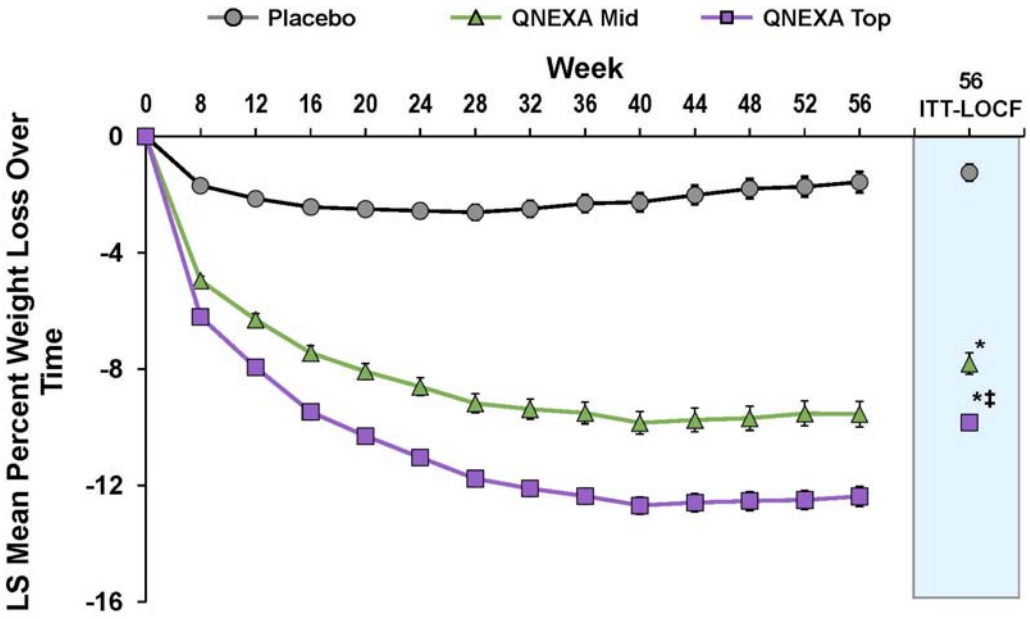
Figure 9 and **Figure 10** show the LS mean percent weight loss over one year of treatment by treatment group for the ITT-LOCF set in pivotal studies OB-302 and OB-303, respectively.

Figure 9. Percent Weight Loss from Baseline Over Time – Individual Study OB-302 (Completer Population and ITT-LOCF Set)



* p<0.0001 versus placebo; ‡ p<0.0001 versus QNEXA Low Dose.
Completer Population = all observed data for subjects still on drug at the reported time point;
ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Top, 15 mg/92 mg.

Figure 10. Percent Weight Loss from Baseline Over Time – Individual Study OB-303 (Completer Population and ITT-LOCF Set)



* p<0.0001 versus placebo; ‡ p<0.0001 versus QNEXA Mid Dose and QNEXA Top Dose.
Completer Population = all observed data for subjects still on drug at the reported time point;
ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.1.2 Weight Loss by Benchmark Category

Table 3 shows the percentage of subjects in each of the Phase 3 studies with ≥5%, ≥10% and ≥15% weight loss by study endpoint. The 5% categorical weight loss was a co-primary endpoint in all three studies.

Table 3. Percentage of Subjects with ≥5%, ≥10%, and ≥15% Weight Loss at Study Endpoint – Individual Studies OB-302, and OB-303 (ITT-LOCF Set[a])

Analysis Category	OB-301			OB-302			OB-303		
	Placebo	QNEXA Mid	QNEXA Top	Placebo	QNEXA Low	QNEXA Top	Placebo	QNEXA Mid	QNEXA Top
	N=103	N=103	N=103	N=498	N=234	N=498	N=979	N=488	N=981
≥5% weight loss	15.5	62.1	66.0	17.3	44.9*	66.7*‡	20.8	62.1*	70.0*‡
≥10% weight loss	6.8	38.8	40.8	7.4	18.8*	47.2*‡	7.4	37.3*	47.6*‡
≥15% weight loss	--	--	--	3.4	7.3†	32.3*‡	2.9	19.3*	28.8*‡

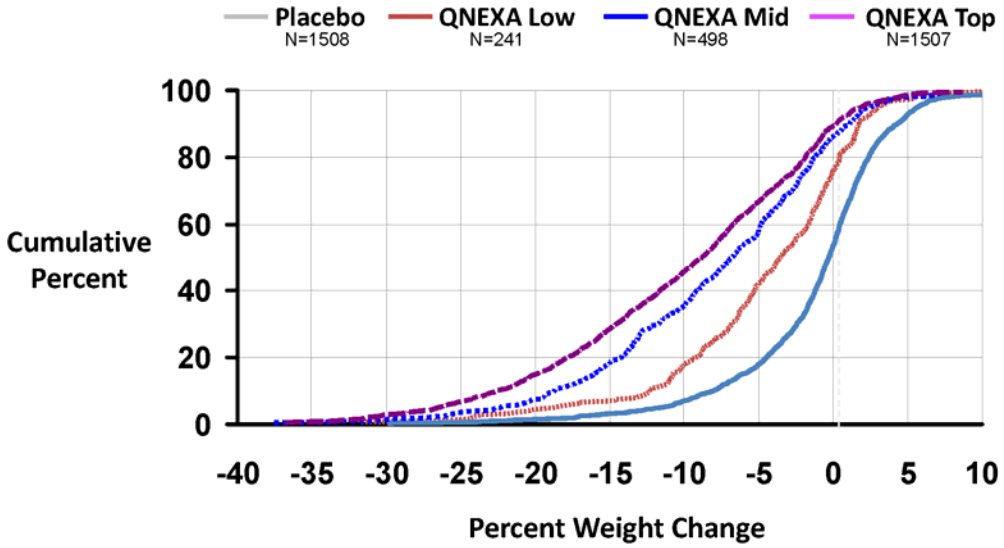
a. ITT-LOCF analysis includes the last post-dose measurement for all subjects in the ITT set, regardless of whether or not the subject was on study drug.
*p<0.001 versus placebo.
†p<0.05 versus placebo.
‡p<0.01 versus QNEXA Low (OB-302) or QNEXA Mid (OB-303).
ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In study OB-301, the 6-month study, treatment with QNEXA Top dose and Mid dose both resulted in a higher proportion of subjects attaining weight loss of ≥5% and ≥10%, respectively, from baseline at Week 28 compared with the individual components phentermine or topiramate, or with placebo.

Similar results with respect to proportions of subjects attaining weight loss benchmarks were obtained in year-long studies OB-302 and OB-303. The percent of subjects with ≥5%, ≥10%, and ≥15% weight loss was significantly greater in subjects treated with QNEXA compared with placebo at Week 56. In addition, the proportion of subjects in each weight loss category increased according to QNEXA dose.

The cumulative distribution frequency plots for the 56-week Phase 3 studies, shown in **Figure 11**, demonstrate that regardless of the benchmark selected, the percentage of subjects achieving this benchmark increased as the dose of QNEXA increased.

Figure 11. Cumulative Distribution of Percent Weight Change at Week 56 (ITT-LOCF Set)



ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.2 Primary Endpoint Sensitivity Analyses: Weight Loss in Important Subgroups

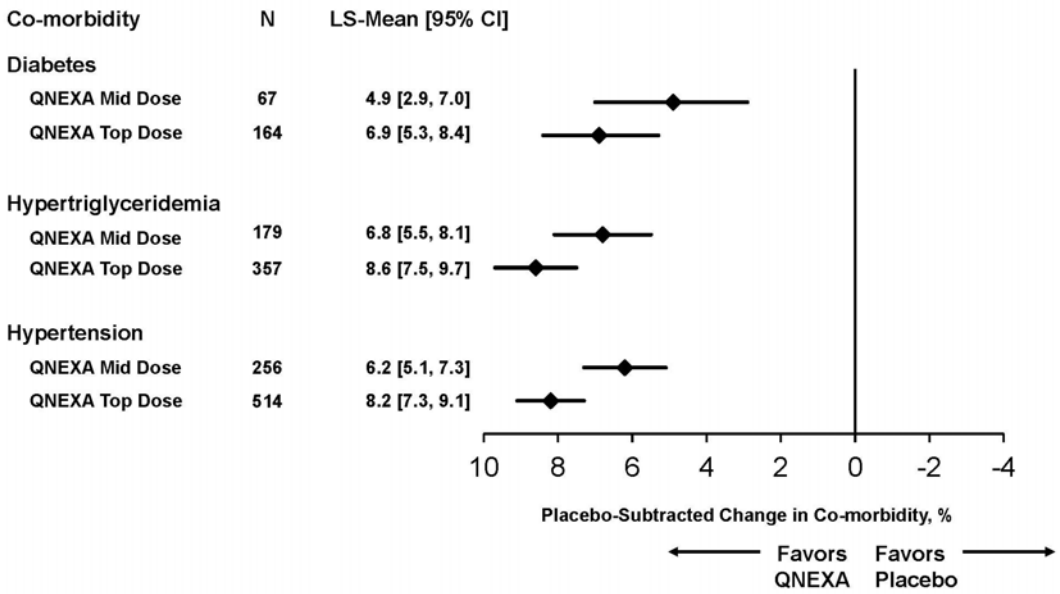
2.5.2.1 Weight Loss by Demographic Subgroups

Subgroup analyses of weight loss efficacy results in studies OB-302 and OB-303, in which subjects were stratified according to baseline BMI, age, race, or sex, indicate dose-related weight loss associated with QNEXA therapy, but no differences among demographic subgroups.

2.5.2.2 Weight Loss by Obesity-Related Comorbidity Status at Baseline

Subgroup analysis of subjects with comorbidities in study OB-303, the pivotal study in which these subjects were enrolled, indicate that statistically significantly greater weight loss was observed in subjects treated with QNEXA compared with subjects treated with placebo. Weight loss in subpopulations with diabetes, hypertriglyceridemia, or hypertension at baseline was comparable to the weight loss obtained with QNEXA in the total population **(Figure 12)**.

Figure 12. Placebo-Subtracted Weight Loss from Baseline at Study Endpoint, by Baseline Comorbidity Status, in Subjects Treated with QNEXA – Study OB-303 (ITT-LOCF Set)

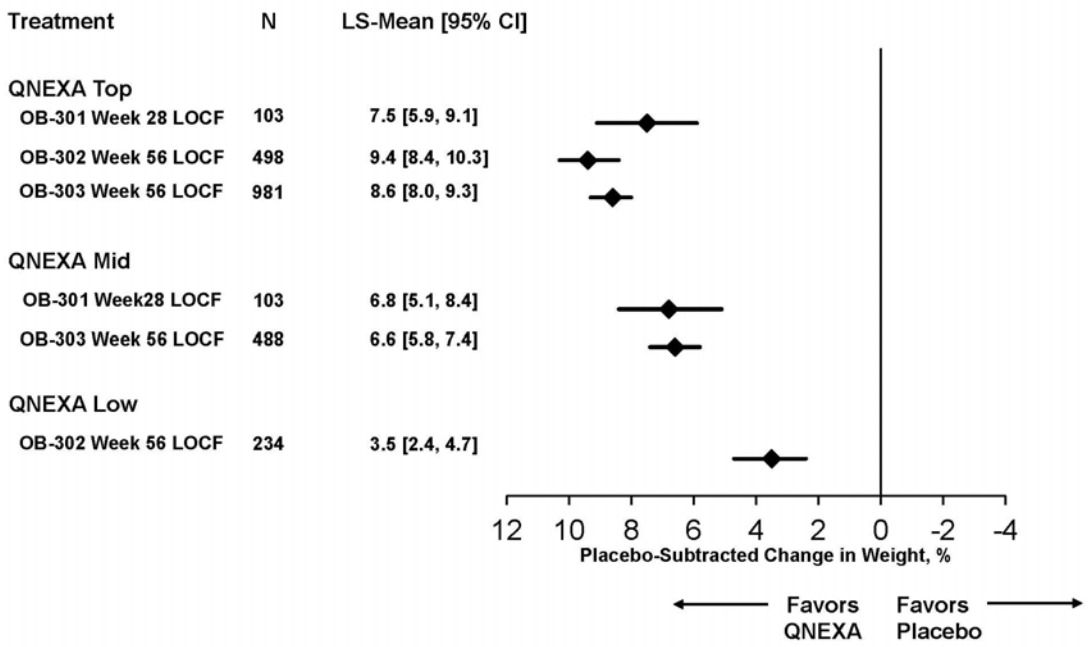


CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.3 Summary of Weight Loss Efficacy

Figure 13 shows the results for percent weight loss, relative to placebo, at study endpoint for the ITT-LOCF set across the Phase 3 studies. The results demonstrate consistency of effect across trials as well as dose responsiveness of the effect of QNEXA on weight loss.

Figure 13. Placebo-Subtracted Weight Loss from Baseline at Study Endpoint in Subjects Treated with QNEXA – Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)



CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Placebo-subtracted weight loss results across each of the Phase 3 studies were not only statistically significant, but compare favorably to the expected results of currently approved weight loss therapies. According to the Cochrane Collaboration review of long-term pharmacotherapy for obesity and overweight, the recommended dose of Xenical® (orlistat) is associated with a placebo-subtracted weight loss of approximately 2.9% (95% CI, 2.5–3.4%; 13 studies) after 1 year of treatment (Padwal 2003). This is approximately the same weight loss as QNEXA Low dose. Treatment with QNEXA Mid dose and QNEXA Top dose has been shown to result in placebo-subtracted weight losses of 6.6% to 6.8% and 8.6% to 9.4%, respectively, after one year of treatment.

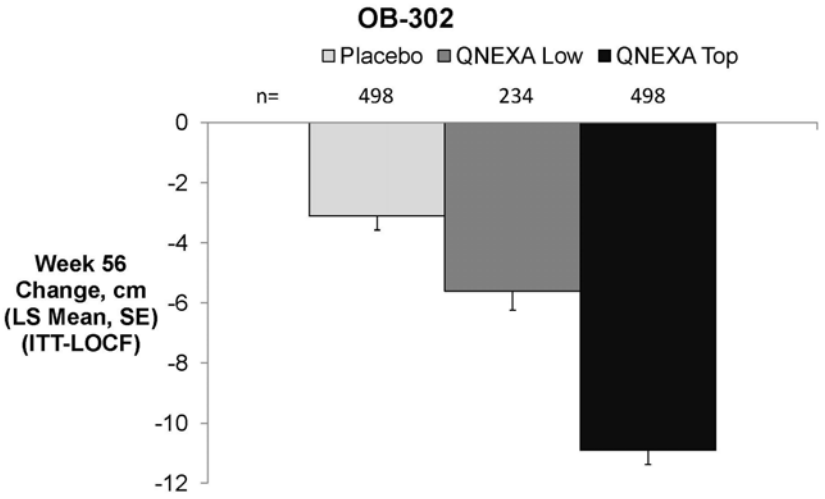
2.5.4 Secondary and Exploratory Endpoints Other than Weight Loss

2.5.4.1 Waist Circumference

In study OB-302, the reduction from baseline in LS mean waist circumference at Week 56 was significantly greater in the QNEXA Top dose group (-10.9 cm) and QNEXA Low dose group (-5.6 cm) compared with the placebo group (-3.1 cm) ($p<0.0001$ and $p=0.0006$, respectively).

Results for Study OB-302 is shown in **Figure 14**.

Figure 14. Waist Circumference Change from Baseline at Study Endpoint – Individual Study OB-302 (ITT-LOCF Set)

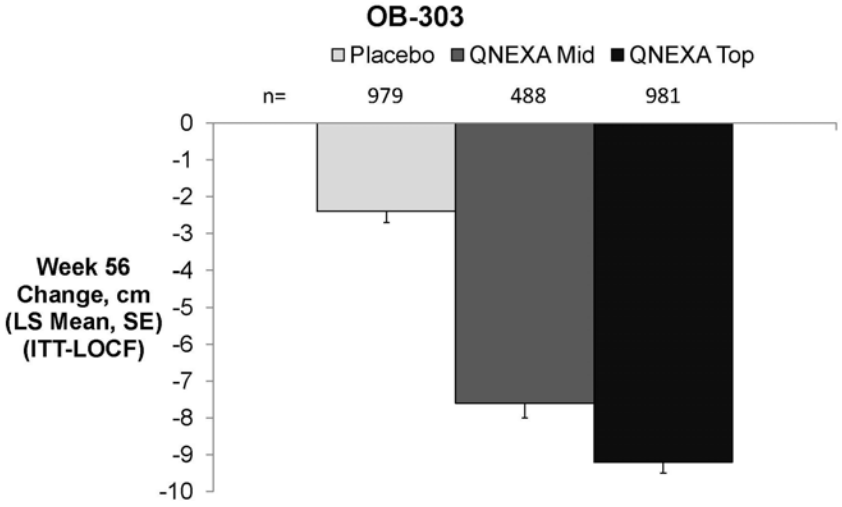


Nominal p<0.0001 (Mid and Top doses), nominal p=0.0006 (Low dose), versus placebo for each.
n = Number of subjects reaching threshold at Week 56.
LS mean, SE, and two-sided p-value are from ANCOVA model with treatment and gender as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares;
QNEXA = fixed-dose combination of phentermine and topiramate; SE = standard error.
QNEXA Low, 3.75 mg/23 mg; QNEXA Top, 15 mg/92 mg.

In study OB-303, the reduction from baseline in waist circumference was significantly greater in the QNEXA Top dose group (-9.2 cm) and the QNEXA Mid dose group (-7.6 cm) compared with placebo group (-2.4 cm) at Week 56 (p<0.0001 versus placebo, in each case).

Results for Study OB-302 are shown in **Figure 15**.

Figure 15. Waist Circumference Change from Baseline at Study Endpoint – Individual Study OB-303 (ITT-LOCF Set)



Nominal p<0.0001 (Mid and Top doses), nominal p=0.0006 (Low dose), versus placebo for each.
n = Number of subjects reaching threshold at Week 56.
LS mean, SE, and two-sided p-value are from ANCOVA model with treatment and gender as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares;
QNEXA = fixed-dose combination of phentermine and topiramate; SE = standard error.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.4.2 Body Composition

A subset of subjects from participating sites in studies OB-302 and OB-303 underwent dual energy x-ray absorptiometry (DEXA) scanning for evaluation of changes in body composition. Mean decreases in percent adiposity and mean increases in percent lean body mass from baseline were larger for the QNEXA Top dose group compared with placebo in the OB-302 subset and larger for both QNEXA groups compared with placebo in the OB-303 subset (**Table 4**).

Table 4. Body Composition Change from Baseline at Week 56 – Individual Studies OB-302, and OB-303 – ITT Subjects Participating in DEXA Absorptiometry Substudy

	LS Mean (SE)[b] OB-302			LS Mean (SE)[b] OB-303		
	Placebo (n^a=29)	QNEXA Low (n^a=14)	QNEXA Top (n^a=30)	Placebo (n^a=42)	QNEXA Low (n^a=27)	QNEXA Top (n^a=60)
% adiposity	- 1.7 (0.66)	- 1.5 (0.95)	- 3.3 (0.65)	- 0.8 (0.52)	- 2.9 (0.65)	- 4.2 (0.44)
% lean body mass	1.6 (0.61)	1.3 (0.89)	2.9 (0.60)	0.8 (0.49)	2.6 (0.62)	3.8 (0.41)

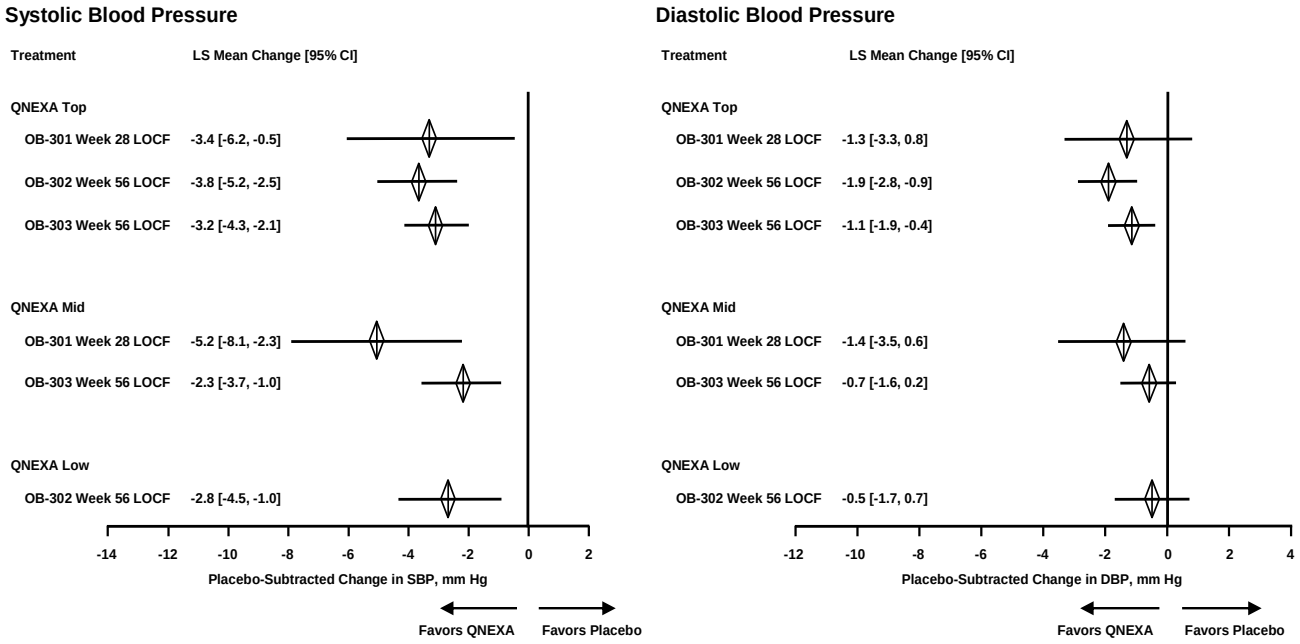
a. n is the number of subjects with values at both time points.
b. LS mean, SE, and two-sided p-value from ANCOVA model with treatment as a fixed effect and baseline as a covariate.
LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate; SE = standard error.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.4.3 Obesity-Related Comorbidities

2.5.4.3.1 Blood Pressure

Reductions from baseline in systolic and diastolic blood pressure (SBP and DBP, respectively) were consistently observed from weight loss in subjects treated with QNEXA compared with subjects treated with placebo at study endpoint across all Phase 3 studies **(Figure 16)**.

Figure 16. Placebo-Subtracted Systolic and Diastolic Blood Pressure Change from Baseline at Study Endpoint in Subjects Treated with QNEXA – Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)

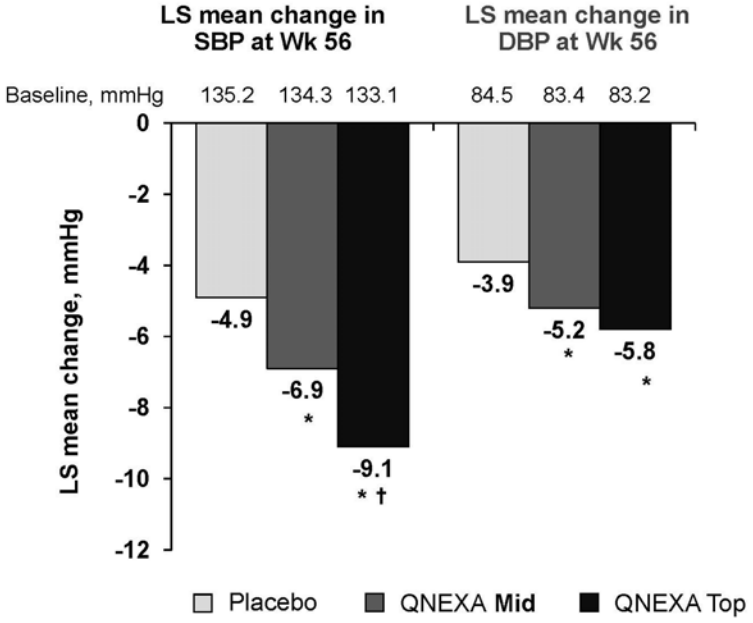


CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In study OB-303, 1286 (52.5%) subjects met the protocol-specified criteria for hypertension (SBP 140-160 mmHg [130-160 mmHg, if diabetic]; DBP 90-100 mmHg [85-100 mmHg, if diabetic]; or use of two or more anti-hypertensive medications to control blood pressure). For the subpopulation of subjects with hypertension, the LS mean percent weight loss at Week 56 with LOCF was 10.1% with QNEXA Top dose treatment, 8.2% with QNEXA Mid dose, and 1.9% with placebo. These results were similar to those observed for the overall OB-303 ITT set (9.8% with QNEXA Top dose, 7.8% with QNEXA Mid dose, and 1.2% with placebo).

Figure 17 presents the results for changes in SBP and DBP at Week 56 with LOCF for the subgroups of subjects with hypertension at baseline in study OB-303. The largest mean reductions in blood pressure were observed in the subpopulation of subjects with hypertension and in subjects with baseline SBP and DBP in the upper quartiles of the baseline distribution.

Figure 17. Blood Pressure Change from Baseline at Week 56 in Subjects with Hypertension – Study OB-303 (ITT-LOCF Set)



*nominal p<0.05 versus placebo; †nominal p<0.001 versus placebo.
BL = baseline; BP = blood pressure; ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Among subjects with hypertension, 3.9% and 4.3% of QNEXA Mid dose and QNEXA Top dose subjects, compared with 8.1% of placebo subjects, started new anti-hypertensive medications. Conversely, 10.5% and 14.8% of QNEXA Mid dose and QNEXA Top dose subjects, compared with 4.7% of placebo subjects, discontinued existing anti-hypertensive medications (**Table 5**).

Table 5. Changes in Concomitant Anti-hypertensive Medications at End of Study in Subjects with Hypertension – Study OB-303 (ITT-LOCF Set)

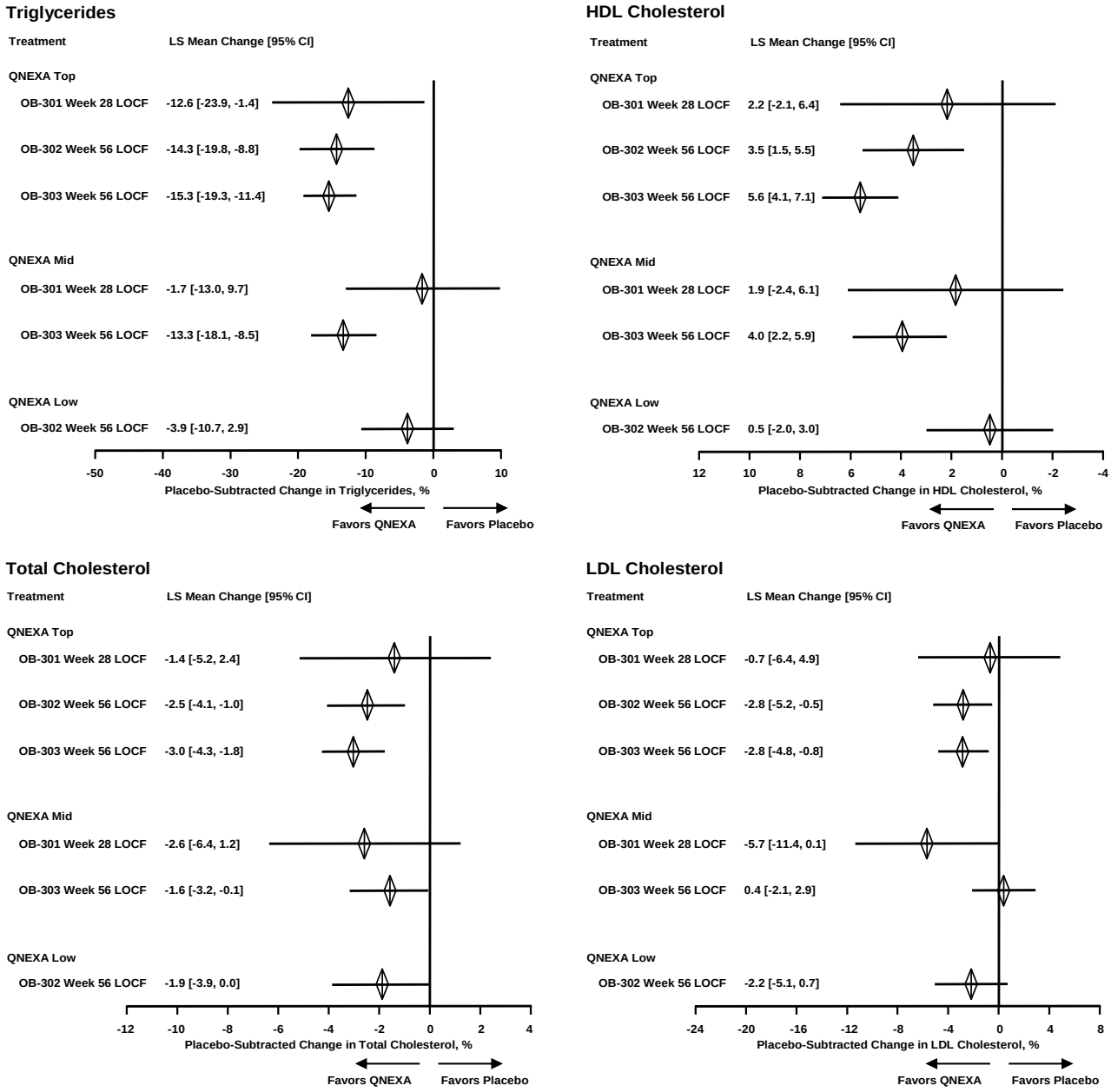
Treatment	N	Number of Medications Per Subject			Number (%) of Subjects		
		Baseline Mean (SD)	End of Study Mean (SD)	Change Mean (SD)	% Subjects with Decrease	% Subjects with No change	% Subjects with Increase
Placebo	516	1.38 (1.058)	1.42 (1.065)	0.04 (0.421)	24 (4.7)	450 (87.2)	42 (8.1)
QNEXA Mid	256	1.43 (1.057)	1.35 (1.044)	-0.09 (0.443)	27 (10.5)	219 (85.5)	10 (3.9)
QNEXA Top	514	1.59 (1.030)	1.46 (1.010)	-0.13 (0.528)	76 (14.8)	416 (80.9)	22 (4.3)

QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.4.3.2 Lipid Parameters

Mean TG, HDL-C, TC, and LDL-C levels were improved from baseline in subjects treated with QNEXA, compared with subjects treated with placebo, at end of study across all Phase 3 trials **(Figure 18)**.

Figure 18. Placebo-Subtracted Lipid Parameters Changes from Baseline at Study Endpoint in Subjects Treated with QNEXA – Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)



CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In subjects treated with QNEXA Top dose, TG levels were significantly lower than those of subjects treated with placebo across all three Phase 3 trials. In subjects treated with QNEXA Top dose, TC, HDL-C, and LDL-C levels were significantly improved over those of subjects treated with placebo in studies OB-302 and OB-303.

In study OB-303, 885 (36.2%) subjects met the protocol-specified criteria for hypertriglyceridemia (TG ≥200 and ≤400 mg/dL, or use of more than 1 lipid-lowering

medication). For these subjects, treatment with either QNEXA Mid dose or QNEXA Top dose resulted in significant decreases in TG levels and significant increases in HDL-C levels relative to placebo due to weight loss. Treatment with QNEXA Top dose also resulted in a significant decrease in TC relative to placebo (**Table 6**).

Table 6. Lipid Parameters Change from Baseline at Week 56 in Subjects with Hypertriglyceridemia – Study OB-303 (ITT-LOCF Set)

	Placebo (n=336)		QNEXA Mid (n=171)		QNEXA Top (n=348)	
	Baseline[a]	Week 56 Percent Change[b]	Baseline[a]	Week 56 Percent Change[b]	Baseline[a]	Week 56 Percent Change[b]
Triglycerides, mg/dL	238.4	-8.8	229.2	-24.1*	229.2	-25.6*
LDL-C cholesterol, mg/dL**	124.0	-3.6	114.6	0.7	122.2	-4.3
Total cholesterol, mg/dL	214.3	-4.9	203.4	-5.7	211.9	-7.8†
HDL-C cholesterol, mg/dL	42.5	2.8	42.9	9.5*	43.9	10.7*

a. Mean baseline values.
b. Least-squares mean percent changes from baseline to Week 56 with LOCF.
*p<0.001 versus placebo.
†p<0.05 versus placebo.
** for LDL-C: n for placebo = 331, n for top dose = 345
HDL-C = high-density lipoprotein; ITT-LOCF = intent-to-treat–last observation carried forward;
LDL-C = low-density lipoprotein; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

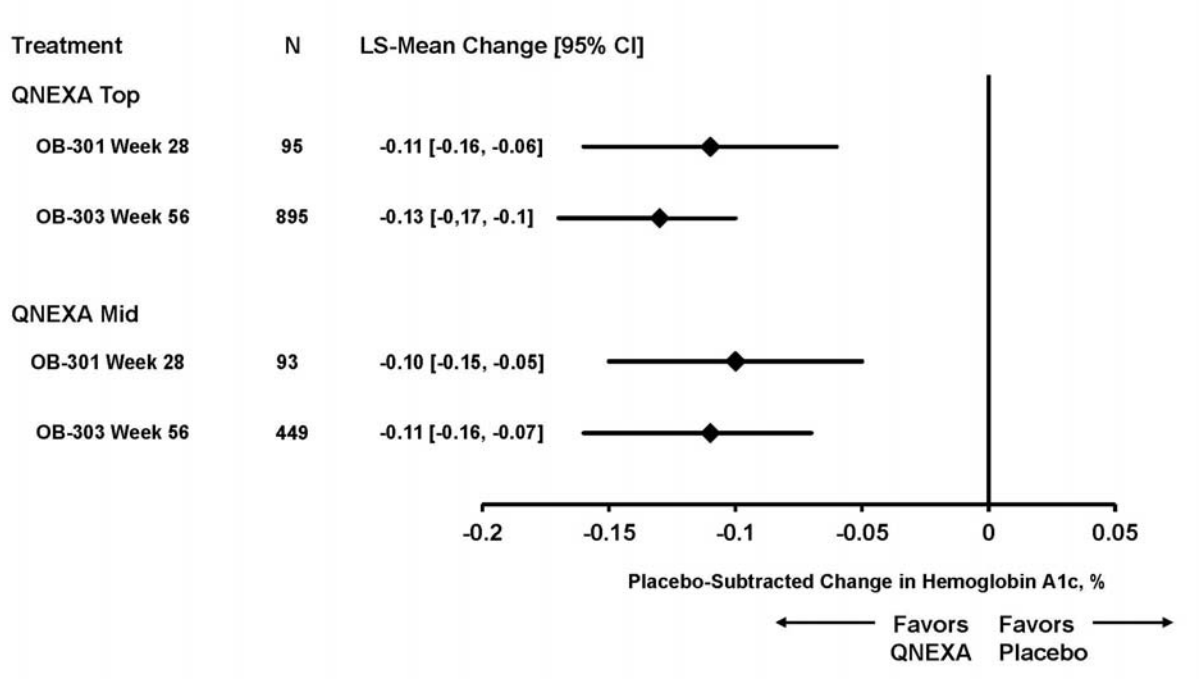
2.5.4.3.3 Glycemic Parameters

Treatment with QNEXA in the Phase 3 studies improved the glycemic profiles of all subjects regardless of whether baseline status was normal, pre-diabetic, or diabetic. Data are presented below for changes in HbA_{1c} and fasting serum glucose in all subjects and in the subgroup of subjects who had diabetes at baseline.

2.5.4.3.3.1 HbA_{1c} and Fasting Serum Glucose

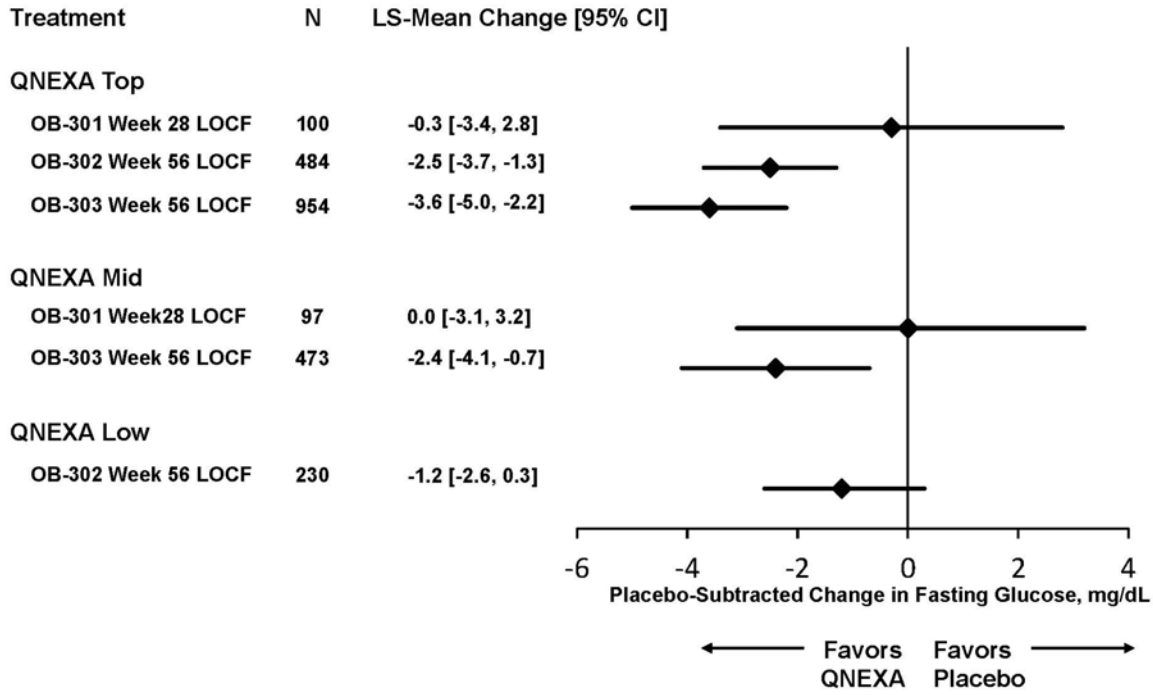
Significant improvements in HbA_{1c} from baseline at study endpoint relative to placebo, occurred in both trials OB-301 and OB-303 in subjects treated with QNEXA. HbA_{1c} was not measured in study OB-302 since the study enrolled only non-diabetic subjects. Significant improvements in fasting serum glucose from baseline at study endpoint, relative to placebo, occurred across trials OB-302 and OB-303 in subjects treated with QNEXA Top dose. (**Figure 19** and **Figure 20**).

Figure 19. Placebo-Subtracted Hemoglobin A_{1c} Change from Baseline at Study Endpoint in Subjects Treated with QNEXA – Individual Studies OB-301, and OB-303 (ITT-LOCF Set)



CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Figure 20. Placebo-Subtracted Fasting Serum Glucose Change from Baseline at Study Endpoint in Subjects Treated with QNEXA – Individual Studies OB-301, OB-302, and OB-303 (ITT-LOCF Set)



CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.4.3.3.2 Results in Subjects with Diabetes at Baseline

In study OB-303, 388 (15.8%) subjects met the protocol-specified criteria for diabetes (fasting blood glucose ≥126 mg/dL, 2-hour post-oral glucose tolerance test [OGTT] ≥200 mg/dL or diagnosis of type 2 diabetes managed with lifestyle measures or metformin monotherapy) at baseline. For these subjects, treatment with QNEXA resulted in weight loss and significant decreases in HbA_{1c} relative to placebo and larger, though not statistically significant, decreases in fasting serum glucose than placebo (**Table 7**). Moreover, 4.5% of QNEXA Mid dose and 4.3% of QNEXA Top dose-treated subjects, compared with 14.6% of placebo-treated subjects started new antidiabetic medications while 3.0%, 3.7% and 2.5% of QNEXA Mid dose, QNEXA Top dose and placebo-treated subjects, respectively, discontinued existing antidiabetic medications.

Table 7. Hemoglobin A_{1c}, Fasting Glucose Changes from Baseline at Study Endpoint in Subjects With Diabetes – Individual Studies OB-303, and OB-202 (ITT-LOCF Set)

	OB-303			OB-202	
	Placebo	QNEXA Mid	QNEXA Top	Placebo	PHEN/TPM 15/100
Baseline HbA_{1c}, %	n=144	n=63	n=150	n=101	n=99
	6.8	6.8	6.8	8.6	8.7
LS Mean change in HbA_{1c}, %	-0.1	-0.4*	-0.4*	-0.6	-1.1†
Baseline fasting glucose, mg/dL	n=153	n=65	n=155	n=101	n=99
	136.7	134.2	131.1	174.0	174.7
LS Mean change in fasting glucose, mg/dL	-5.6	-9.7	-11.9	-7.6	-32.6‡
Subjects with:	n=157	n=67	n=164	n=101	n=99
Antidiabetic medications added, %	14.6	4.5	4.3	27.7	18.2
Antidiabetic medications discontinued, %	2.5	3.0	3.7	5.0	8.1

*p<0.05 versus placebo.
†p=0.0007 versus placebo.
‡p=0.0001 versus placebo.
HbA_{1c} = hemoglobin A_{1c}; ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Also presented in **Table 7** are the results from study OB-202, a Phase 2, randomized, double-blind, placebo-controlled, multicenter trial comparing phentermine/topiramate combination therapy with placebo in adult subjects ≤70 years of age who had a BMI ≥27 kg/m^2 and ≤45 kg/m^2 and type 2 diabetes that was controlled by diet or oral antidiabetic medications after 28 weeks of treatment. The primary endpoint was change in HbA_{1c}. A total of 210 eligible subjects were randomized to receive daily treatment with placebo or the combination of phentermine 15 mg and topiramate 100 mg.

Enrolled subjects represented a wide spectrum of the diabetic population in terms of duration and severity of disease and in terms of medications to control disease permitted at baseline. Notably, this study included a population of subjects with more advanced diabetes than study OB-303. Overall, 32% of subjects had been diagnosed with diabetes for 5 to 10 years and 27% for more than 10 years. Subjects enrolled in the study were required to have a baseline HbA_{1c} of 7% to 12%, inclusive and the mean for the study was 8.7%. Forty-seven percent of subjects were taking two or more diabetic medications and 20% of subjects were naïve to diabetic medication. Additionally, the study group was racially diverse, and most subjects reported Hispanic or Latino ethnicity.

As seen in **Table 7**, the LS mean change in HbA_{1c} from baseline (mean 8.7%) to Week 28 was -1.1% for the phentermine/topiramate 15 mg/100 mg group and -0.6% for the placebo group. The difference from baseline at Week 28 between active treatment and placebo was significant. This HbA_{1c} reduction was greater than the reduction obtained in subjects in study OB-303. Moreover, in study OB-202, the percentage of subjects with an increase in the number of concomitant antidiabetic medications from baseline to end of study was higher in the placebo group than in the active treatment group, and a decrease in the number of

concomitant antidiabetic medications was higher in the phentermine/topiramate treatment group than in the placebo group.

A large proportion of the OB-303 study population had impaired fasting glucose or impaired glucose tolerance at baseline. In this study, QNEXA treatment resulted in weight related improvements in fasting insulin levels, decreases in insulin resistance as measured by homeostatic model assessment of insulin resistance (HOMA-IR), and increases in insulin sensitivity during oral glucose tolerance testing (**Table 8**).

Table 8. Fasting Insulin and Insulin Sensitivity Parameters Changes from Baseline at Week 56 – Study OB-303 (ITT-LOCF Set)

	Placebo[a]		QNEXA Mid[b]		QNEXA Top[c]	
Parameter	Baseline[d]	Week 56 Change[e]	Baseline[d]	Week 56 Change[e]	Baseline[d]	Week 56 Change[e]
Fasting insulin, µIU/mL	17.8	0.7	18.0	-3.5*	18.4	-4.0*
HOMA-IR	5.15	0.46	4.94	-0.93*	5.30	-1.07*
Composite whole-body insulin sensitivity index	3.54	0.5	3.36	1.7*	3.65	2.0*

a. N = 925 for fasting insulin and HOMA-IR; N = 918 for composite whole-body insulin sensitivity index.
b. N = 464 for fasting insulin and HOMA-IR; N = 459 for composite whole-body insulin sensitivity index.
c. N = 937 for fasting insulin and HOMA-IR; N = 925 for composite whole-body insulin sensitivity index.
d. Mean baseline values.
e. Least-squares mean changes from baseline to Week 56 with LOCF.
*p<0.001 versus placebo.
HOMA-IR = homeostasis model assessment–insulin resistance; ITT-LOCF = intent-to-treat–last observation carried forward; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

2.5.4.3.3.3 Onset of Type 2 Diabetes

Consistent with the changes in fasting insulin and insulin sensitivity parameters discussed above, QNEXA demonstrated a benefit in avoidance of progression to type 2 diabetes during the Phase 3 studies. In analyses of all subjects treated in study OB-303, both QNEXA Mid and Top dose treatment resulted in significant and clinically meaningful reductions in fasting insulin and insulin resistance. Moreover, among subjects without a diagnosis of type 2 diabetes at study entry, annualized incidence of progression to type 2 diabetes, based on 2 or more consecutive visits with fasting glucose levels of ≥126 mg/dL or 2-hour post-oral glucose tolerance test [(OGTT)] ≥200 mg/dL, was observed in 30 placebo-treated subjects with an annualized incidence rate of 4.5% compared with 14 subjects in the QNEXA Top dose group with an annualized incidence rate of 1.9%, indicating a 58% decrease in the annualized incidence of new-onset type 2 diabetes in these study subjects due to weight loss.

2.5.4.3.4 Summary of Efficacy on Obesity-Related Comorbidities

Improvements in obesity-related comorbidities, such as cardiovascular and lipid comorbidities, were consistently demonstrated in QNEXA treatment groups across studies and across the entire population. At 1 year, treatment with any of the three doses of QNEXA resulted in significant decreases from baseline in systolic blood pressure compared with

placebo. Significant improvements were also demonstrated in lipid profiles, glycemic indices, and inflammatory markers. Significant effects on weight-related comorbidities were most frequent in the QNEXA Top dose group.

In subjects with comorbidities at baseline, greater and dose-related improvements in weight related cardiovascular, metabolic, and inflammatory disease markers were achieved with QNEXA than with placebo. In the case of subgroups of subjects with hypertension or diabetes, QNEXA-related improvements in blood pressure and glycemic parameters occurred concomitantly with reductions in medications taken by subjects to treat these comorbidities. In general, a greater burden of obesity-related comorbidity at baseline was associated with a greater degree of disease improvement with QNEXA therapy, as well as a significant reduction in medications required to treat the associated comorbidity. Based in part on these data, VIVUS has designed a Phase 4 cardiovascular outcomes trial intended to evaluate the safety and efficacy of QNEXA in reducing major cardiovascular adverse events in obese patients. A synopsis of the study protocol is provided in **Appendix 4**.

2.5.4.4 Biomarkers of Cardiovascular Disease Risk

High-sensitivity (hs)-CRP values were determined in subjects included in the 1-Year Cohort (**Table 9**). A total of 3157 subjects had both baseline and Week 56/ET hs-CRP values available (1179 on placebo and 1978 on any dose of QNEXA). Mean baseline hs-CRP was 7.28 mg/L (SD ± 9.96) in the 1-Year Cohort (median 4.8 mg/L), indicating an elevated level of cardiovascular risk. By Week 56/ET, hs-CRP was reduced significantly in placebo, QNEXA Mid dose, and QNEXA Top dose groups, but the magnitude of reduction was greater in the QNEXA Mid and Top dose groups (-2.8 and -2.8 mg/L, respectively) than in the placebo group (-0.7 mg/L). The change in hs-CRP in the Mid dose and Top dose groups represented a mean reduction of approximately 39% from baseline values.

Table 9. High-Sensitivity C-Reactive Protein Change from Baseline at Week 56/ET in All Subjects and Subjects with Baseline Value >3 mg/L – Studies OB-202, DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

All subjects				
Time Point	**Placebo (N=1,179)**	**QNEXA Low (N=181)**	**QNEXA Mid (N=440)**	**QNEXA Top (N=1,357)**
Baseline hs-CRP, mg/L[a]	7.2	8.9	7.0	7.2
Week 56/ET, mg/L[a]	6.5	8.4	4.2	4.5
Week 56/ET change, mg/L[b]	-0.7	-0.5	-2.8	-2.8
Subjects with baseline value >3 mg/L				
Time Point	**Placebo (N=777)**	**QNEXA Low (N=147)**	**QNEXA Mid (N=275)**	**QNEXA Top (N=896)**
Baseline hs-CRP, mg/L[a]	10.1	10.6	10.2	10.1
Week 56/ET, mg/L[a]	8.5	9.7	5.7	5.8
Week 56/ET change, mg/L[b]	-1.6	-0.9	-4.6	-4.4

a. Mean values.
b. Mean changes from baseline to Week 56/ET.
ET = early termination; hs-CRP = high-sensitivity C-reactive protein; ITT-LOCF = intent-to-treat–last observation carried forward; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In study OB-303, the mean changes in C-reactive protein, adiponectin, and fibrinogen were significant for all treatment groups. Significantly greater reductions in C-reactive protein were observed with QNEXA Top dose and QNEXA Mid dose relative to placebo. The improvements in adiponectin and fibrinogen were also greater with QNEXA Top dose and QNEXA Mid dose than with placebo; however, formal treatment comparisons were not performed.

2.5.4.5 Liver Enzymes

In studies OB-302 and OB-303, LS mean decreases from baseline in alanine transaminase (ALT) were larger for the QNEXA groups than for the placebo groups at Week 56 (**Table 10**). Mean decreases in aspartate transaminase (AST) were only observed in the QNEXA Top dose group in study OB-302. In study OB-303 decreases from baseline in AST were also observed for the QNEXA groups, whereas increases from baseline were observed for the placebo group.

Table 10. Alanine Transaminase and Aspartate Transaminase Changes from Baseline at Study Endpoint – Individual Studies OB-302, and OB-303 (ITT-LOCF Set)

Parameter	OB-302			OB-303		
	Change at Week 56 (LOCF)[a]			Change at Week 56 (LOCF)[b]		
Treatment	N	Baseline	LS Mean (SE)	n	Baseline	LS Mean (SE)
Alanine transaminase, mU/mL						
Placebo	479	26.3	-0.7 (0.71)	939	30.6	-0.8 (0.60)
QNEXA Low	230	25.7	-1.5 (0.95)*	--	--	--
QNEXA Mid	--	--	--	475	31.5	-4.0 (0.79)††
QNEXA Top	486	27.3	-2.2 (0.71)	964	30.7	-3.3 (0.59)††
Aspartate transaminase, mU/mL						
Placebo	478	21.8	0.7 (0.87)	940	24.7	0.9 (0.48)
QNEXA Low	230	21.4	1.9 (1.17)	--	--	--
QNEXA Mid	--	--	--	475	25.1	-0.7 (0.63)*
QNEXA Top	486	22.8	-0.7 (0.87)	964	24.5	-0.7 (0.47)†

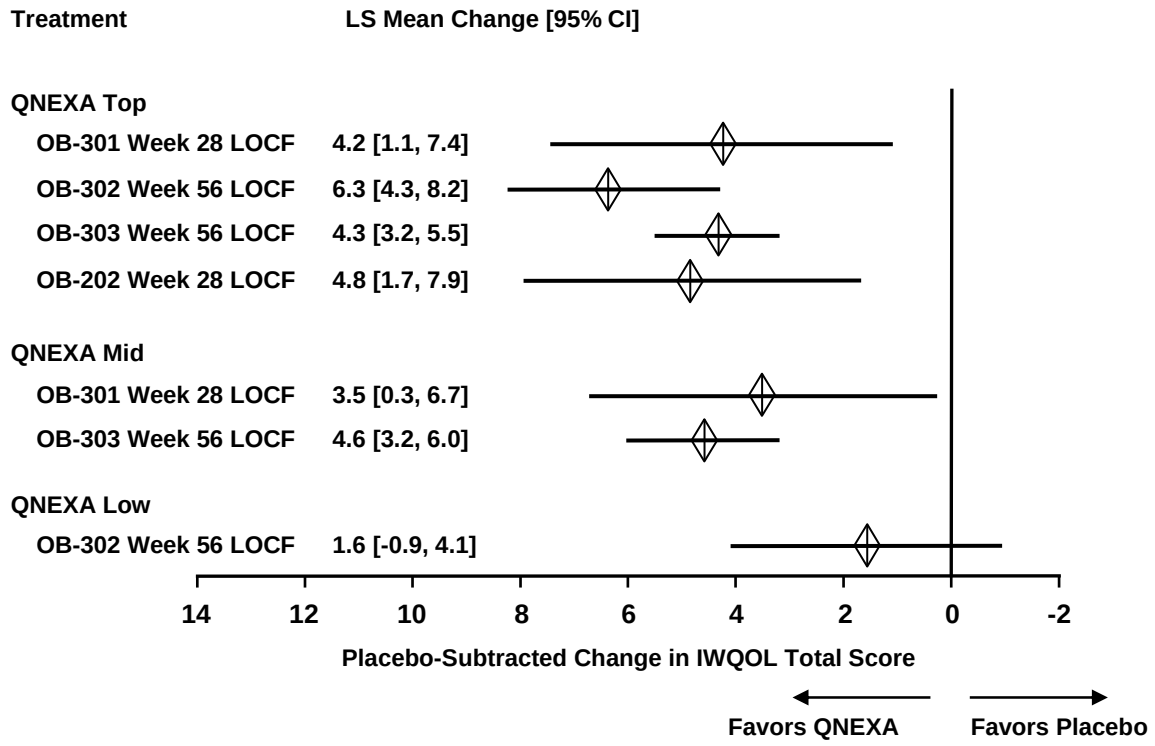
* p<0.05 versus placebo
† p<0.01 versus placebo
†† p<0.001 versus placebo
a. LS mean, SE, and two-sided p-value are from ANCOVA model with treatment and gender as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
b. LS mean, SE, and two-sided p-value are from ANCOVA model with treatment, gender, and diabetic status as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares;
QNEXA = fixed-dose combination of phentermine and topiramate; SE = standard error.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In subjects with elevated LFT (liver function test) values at baseline (upper quartile) subjects treated with QNEXA Mid and Top dose demonstrated significantly greater improvements in ALT values from baseline compared with subjects treated with placebo.

2.5.4.6 Quality of Life

Subjects in studies OB-301, OB-302, and OB-303 were evaluated with respect to changes in quality of life. The Impact of Weight on Quality of Life (IWQOL)-Lite© Questionnaire is a 31-item, self-administered instrument designed to evaluate the impact of excess weight on quality-of-life domains, including physical function, self-esteem, sexual life, public distress, and work. The IWQOL Questionnaire was completed by subjects at screening, at Week 28, and at Week 56 or early termination. Scaled scores range from 1 to 100, with higher scores indicating better quality of life and composite scores reflecting overall performance within individual domains. Consistent and significant improvements from baseline in composite scores compared with placebo were observed in subjects treated with QNEXA Top dose across trials OB-301, OB-302, and OB-303 **(Figure 21)**. Improvements were also observed for QNEXA Mid and Low dose in the trials in which these doses were included. Changes of the greatest magnitude were observed in the domains of self-esteem and work function.

Figure 21. Placebo-Subtracted IWQOL Total Score Change from Baseline at Study Endpoint in Subjects Treated with QNEXA – Individual Studies OB-202, OB-301, OB-302, and OB-303 (ITT-LOCF Set)



CI = confidence interval; ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

The Short Form (SF)-36 questionnaire is an instrument designed to evaluate general health, and includes the domains of general health, physical functioning, physical role, bodily pain, vitality, social functioning, emotional role, and mental health. Scaled scores range from 1 to 100, with higher scores indicating improved functional health and well-being. The SF-36 questionnaire was administered in study OB-303, wherein scores improved significantly from baseline versus placebo at Week 56 in physical domains (physical functioning, physical role, bodily pain, general health, and vitality) in subjects who were treated with QNEXA Mid dose or QNEXA Top dose. Effects of QNEXA were neutral for social functioning as well as emotional role and mental health.

3 INTEGRATED SAFETY OVERVIEW

QNEXA is a combination of phentermine and topiramate, in an extended-release formulation, that contains lower doses of these components than are currently marketed as monotherapies for weight loss (phentermine), epilepsy (topiramate) and migraine prophylaxis (topiramate). The recommended dose of QNEXA contains phentermine 7.5 mg and topiramate 46 mg, which is approximately one-fourth the maximum approved daily dose of phentermine (37.5 mg; 30 mg free base) and one-tenth the maximum approved daily dose of topiramate

(400 mg). Top dose QNEXA (phentermine 15 mg and topiramate 92 mg) contains half of the maximum daily dose of phentermine and approximately one-fourth of the maximum daily dose of topiramate. As such, the side effects of QNEXA therapy are expected to be consistent with those described in the approved labeling for phentermine and topiramate, albeit at a severity consistent with lower doses.

Because the QNEXA nonclinical and clinical programs were presented to EMDAC in 2010, the discussion in this section is limited to a general overview of QNEXA safety from the clinical program. Detailed discussions of cardiac safety and teratogenicity, the subjects of the QNEXA CRL are presented in **Section 5** and **Section 6**, respectively. A summary of psychiatric or cognitive safety is presented in **Appendix 6**, although VIVUS understands that the original NDA provided sufficient data to assess the risks as they were not raised by FDA as QNEXA approvability issues.

3.1 Subject Cohorts

The analysis population for safety summaries was the Safety Set, defined as all randomized subjects who received at least one dose of study drug. The primary analysis cohort discussed in this briefing document is the 1-Year Cohort, which comprises all subjects from studies OB-302 and OB-303 and all subjects who entered study DM-230, the 6-month extension to study OB-202. A 6-Month Cohort, which also includes subjects from study OB-202 and study OB-301, is discussed in the NDA. No meaningful differences were observed in the 6-month cohort compared to those presented below for the 1-year cohort. A 2-Year Cohort was not available at the time of original NDA submission and is discussed below with results of study OB-305.

3.2 Extent of Exposure

A total of 3165 subjects received at least 1 dose of QNEXA in the Phase 1 through Phase 3 clinical studies, and 1893 subjects received placebo **(Table 11)**.

Table 11. Estimated Exposure in QNEXA Clinical Development Program

Study Phase	Number of Subjects					
	QNEXA Low	QNEXA Mid	QNEXA Top	QNEXA Other Doses	QNEXA All Doses	Placebo
Phase 1	125	107[a]	225[b]	195	527	98
Phase 2	--	--	177	--	177	178
Phase 3	241	605	1,615	--	2,461	1,617
Program Total	366	712	2,017	195	3,165	1,893

[a]Dose includes 7.5 mg/50 mg.
[b]Dose includes 15 mg/100 mg.
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Extent of exposure to study drug was calculated as last dose date of double-blind study drug minus first dose date of double-blind study drug + 1. No adjustments to extent of exposure for

dose interruptions or alternative dosing strategies were made. Extent of exposure was summarized with descriptive statistics by treatment group, combined QNEXA group, and overall for the 1-Year Cohort.

Overall mean exposure to QNEXA for the 1-Year Cohort was 297.7 days, and overall median exposure to QNEXA was 392.0 days. Mean days of exposure to study drug was similar for the treatment groups. In total, 2373 (61.2%) subjects in the 1-Year Cohort had more than 52 weeks of exposure to QNEXA. Exposure to study drug was similar for the treatment groups.

Table 12 summarizes extent of exposure to study drug for the 1-Year Cohort.

Table 12. Extent of Exposure to Study Drug – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set 1-Year Cohort)

Exposure	Placebo (N=1,561)	QNEXA Low (N=240)	QNEXA Mid (N=498)	QNEXA Top (N=1,580)	QNEXA All Doses (N=2,318)
Extent of exposure, days					
Mean (SD)	268.8 (152.82)	282.2 (148.36)	308.2 (142.35)	296.8 (147.52)	297.7 (146.62)
Median	389.0	391.0	392.0	392.0	392.0
Specified exposure range, n (%)					
≤24 weeks	518 (33.2)	73 (30.4)	109 (21.9)	386 (24.4)	568 (24.5)
≥ 24 weeks to ≤52 weeks	181 (11.6)	24 (10.0)	42 (8.4)	173 (10.9)	239 (10.3)
>52 weeks	862 (55.2)	143 (59.6)	347 (69.7)	1,021 (64.6)	1,511 (65.2)

QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.3 Subject Disposition

Table 13 summarizes subject disposition for the 1-Year Cohort, which comprised 3,884 subjects randomly assigned to treatment groups. Of the 3,884 randomized subjects, 2,342 (60.3%) completed all study visits on study drug and 1,537 (39.6%) discontinued study drug. A higher percentage of subjects in the QNEXA treatment groups than in the placebo group completed the study on study drug (64.0% versus 54.8%). The most common reasons for discontinuation of study drug were AEs (12.7%), loss to follow-up (10.4%), and withdrawal of consent (10.2%). There was a dose-related increase in the percentage of subjects treated with QNEXA who discontinued study drug due to an AE; however, the overall retention rates were higher for all QNEXA treatment groups compared with placebo, with the highest rates shown for QNEXA Mid dose.

Table 13. Subject Disposition – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Disposition	Placebo (N=1,563) n (%)	QNEXA Low (N=241) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,582) n (%)	QNEXA All Doses (N=2321) n (%)	Total (N=3,884) n (%)
Randomized	1563 (100.0)	241 (100.0)	498 (100.0)	1582 (100.0)	2321 (100.0)	3884 (100.0)
Completed all study visits	940 (60.1)	147 (61.0)	374 (75.1)	1141 (72.1)	1662 (71.6)	2602 (67.0)
Discontinued from study	623 (39.9)	94 (39.0)	124 (24.9)	441 (27.9)	658 (28.4)	1282 (33.0)
Subject lost to follow-up	226 (14.5)	31 (12.9)	44 (8.8)	144 (9.1)	219 (9.4)	445 (11.5)
Subject withdrew consent	243 (15.5)	31 (12.9)	40 (8.0)	126 (8.0)	197 (8.5)	440 (11.3)
Adverse event	50 (3.2)	16 (6.6)	21 (4.2)	104 (6.6)	141 (6.1)	191 (4.9)
Lack of efficacy	47 (3.0)	3 (1.2)	1 (0.2)	3 (0.2)	7 (0.3)	54 (1.4)
Protocol noncompliance	14 (0.9)	4 (1.7)	0 (0.0)	16 (1.0)	20 (0.9)	34 (0.9)
Requirement for restricted medication	11 (0.7)	1 (0.4)	7 (1.4)	6 (0.4)	14 (0.6)	25 (0.6)
Pregnancy	2 (0.1)	1 (0.4)	1 (0.2)	16 (1.0)	18 (0.8)	20 (0.5)
Other	30 (1.9)	7 (2.9)	10 (2.0)	23 (1.5)	40 (1.7)	70 (1.8)
Completed all visits on study drug	857 (54.8)	138 (57.3)	344 (69.1)	1003 (63.4)	1485 (64.0)	2342 (60.3)
Discontinued study drug	704 (45.0)	102 (42.3)	154 (30.9)	577 (36.5)	833 (35.9)	1537 (39.6)
Adverse event	132 (8.4)	28 (11.6)	58 (11.6)	276 (17.4)	362 (15.6)	494 (12.7)
Subject lost to follow-up	217 (13.9)	27 (11.2)	41 (8.2)	118 (7.5)	186 (8.0)	403 (10.4)
Subject withdrew consent	225 (14.4)	28 (11.6)	34 (6.8)	108 (6.8)	170 (7.3)	395 (10.2)
Lack of efficacy	63 (4.0)	6 (2.5)	3 (0.6)	11 (0.7)	20 (0.9)	83 (2.1)
Protocol noncompliance	18 (1.2)	5 (2.1)	3 (0.6)	14 (0.9)	22 (0.9)	40 (1.0)
Requirement for restricted medication	17 (1.1)	0 (0.0)	5 (1.0)	6 (0.4)	11 (0.5)	28 (0.7)
Pregnancy	2 (0.1)	1 (0.4)	1 (0.2)	15 (0.9)	17 (0.7)	19 (0.5)
Other	30 (1.9)	7 (2.9)	9 (1.8)	26 (1.6)	42 (1.8)	72 (1.9)
Safety set	1561 (99.9)	240 (99.6)	498 (100.0)	1,580 (99.9)	2,318 (99.9)	3,879 (99.9)

Subjects may be counted in both study and study drug discontinuation sections.
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.4 Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as adverse events that had a start date on or after the first dose date of double-blind study drug and up to 28 days after the last dose date of double-blind study drug.

In addition to the standard presentation of adverse events by system organ class and preferred term, a more focused analysis of adverse events that are either listed on existing product labels for phentermine or topiramate, are associated with specific mechanisms of action (central nervous system activity), or were identified by the FDA as events of potential concern for all antiobesity agents is provided through analysis and presentation of Targeted Medical Events (TMEs) in **Section 3.4.4**. Cardiovascular safety and teratogenic potential, both of

which were the subject of the QNEXA Complete Response Letter, are addressed in **Section 5** and **Section 6** below.

3.4.1 Overview of Adverse Events

Table 14 provides an overall summary of AEs for the 1-Year Cohort. A total of 3,179 (82.0%) subjects had a TEAE; 1,704 (43.9%) subjects had a TEAE that was considered by the investigators to be related to the study drug. The overall incidence of TEAEs and study drug-related TEAEs was higher in all of the QNEXA treatment groups compared with the placebo group. Most TEAEs were mild or moderate in severity. The incidence of severe TEAEs was 8.6% with placebo, 10.4% with QNEXA Low dose 11.0% with QNEXA Mid dose, and 12.5% with QNEXA Top dose.

There was one death during the QNEXA clinical program. This subject was treated with placebo in study OB-303 and died due to cardiopulmonary arrest. A detailed narrative of this event is provided in **Appendix 5**. No deaths occurred in any of the other clinical studies. In total, 143 (3.7%) subjects had an SAE. The incidence of SAEs was similar for the treatment groups

In total, 490 (12.6%) subjects discontinued study drug due to a TEAE, The percentage of subjects who discontinued study drug due to a TEAE was higher in the QNEXA treated group than in the placebo group (QNEXA Top, 17.3%; QNEXA Mid, 11.6%, QNEXA Low, 11.3%; Placebo, 8.4%).

Table 14. Overview of Adverse Events during the Double-Blind Treatment Period – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)	QNEXA All Doses (N=2,318) n (%)	Total (N=3,879) n (%)
Subjects with TEAEs						
Any TEAE	1186 (76.0)	192 (80.0)	424 (85.1)	1377 (87.2)	2318 (86.0)	3179 (82.0)
Any drug-related TEAE	433 (27.7)	100 (41.7)	251 (50.4)	920 (58.2)	1271 (54.8)	1704 (43.9)
Maximum severity of TEAEs						
Mild	491 (31.5)	60 (25.0)	151 (30.3)	524 (33.2)	735 (31.7)	1226 (31.6)
Moderate	561 (35.9)	107 (44.6)	218 (43.8)	656 (41.5)	981 (42.3)	1542 (39.8)
Severe	134 (8.6)	25 (10.4)	55 (11.0)	197 (12.5)	277 (11.8)	411 (10.6)
Deaths	1 (0.1)	0	0	0	0 (0.0)	1 (0.0)
Subjects with SAEs						
Any treatment-emergent SAE	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)	77 (3.3)	129 (3.3)
Any drug-related SAE	6 (0.4)	1 (0.4)	1 (0.2)	8 (0.5)	10 (0.4)	16 (0.4)
Study drug discontinuations due to AEs/SAEs						
Any TEAE	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)	359 (15.5)	490 (12.6)
Any drug-related TEAE	82 (5.3)	19 (7.9)	42 (8.4)	210 (13.3)	271 (11.7)	353 (9.1)
Any SAE	15 (1.0)	2 (0.8)	4 (0.8)	18 (1.1)	24 (1.0)	39 (1.0)

Treatment-emergent adverse events = adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
AE = adverse event; QNEXA = fixed-dose combination of phentermine and topiramate; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.4.2 Common Adverse Events

Table 15 shows the most common TEAEs (experienced by ≥2% of subjects in any treatment group) by system organ class (SOC) and preferred term for the 1-Year Cohort. The incidences of the following TEAEs (preferred terms) were higher in one or more QNEXA groups compared with the placebo group: paresthesia, dry mouth, constipation, dysgeusia, insomnia, dizziness, depression, anxiety, hypoesthesia, alopecia, irritability, disturbance in attention, dry eye, hypokalemia, palpitations, thirst, and decreased appetite.

Table 15. Treatment-Emergent Adverse Events (≥2% of Subjects in Any Treatment Group) by System Organ Class and Preferred Term – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

System Organ Class Preferred Term	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Infections and infestations	644 (41.3)	126 (52.5)	219 (44.0)	730 (46.2)
Upper respiratory tract infection	200 (12.8)	38 (15.8)	61 (12.2)	213 (13.5)
Nasopharyngitis	125 (8.0)	30 (12.5)	53 (10.6)	149 (9.4)
Sinusitis	98 (6.3)	18 (7.5)	34 (6.8)	123 (7.8)
Bronchitis	66 (4.2)	16 (6.7)	22 (4.4)	85 (5.4)
Influenza	69 (4.4)	18 (7.5)	23 (4.6)	69 (4.4)
Urinary tract infection	56 (3.6)	8 (3.3)	26 (5.2)	82 (5.2)
Gastroenteritis viral	45 (2.9)	8 (3.3)	13 (2.6)	43 (2.7)
Gastroenteritis	35 (2.2)	2 (0.8)	11 (2.2)	40 (2.5)
Gastrointestinal disorders	394 (25.2)	73 (30.4)	195 (39.2)	724 (45.8)
Constipation	96 (6.1)	19 (7.9)	75 (15.1)	255 (16.1)
Dry mouth	43 (2.8)	16 (6.7)	67 (13.5)	301 (19.1)
Nausea	69 (4.4)	14 (5.8)	18 (3.6)	114 (7.2)
Diarrhea	76 (4.9)	12 (5.0)	32 (6.4)	89 (5.6)
Dyspepsia	27 (1.7)	5 (2.1)	11 (2.2)	45 (2.8)
Gastroesophageal reflux disease	21 (1.3)	2 (0.8)	16 (3.2)	41 (2.6)
Abdominal pain	30 (1.9)	4 (1.7)	8 (1.6)	31 (2.0)
Vomiting	31 (2.0)	5 (2.1)	7 (1.4)	30 (1.9)
Paresthesia oral	4 (0.3)	1 (0.4)	3 (0.6)	35 (2.2)
Nervous system disorders	317 (20.3)	58 (24.2)	182 (36.5)	685 (43.4)
Paresthesia	30 (1.9)	10 (4.2)	68 (13.7)	315 (19.9)
Headache	145 (9.3)	25 (10.4)	35 (7.0)	167 (10.6)
Dizziness	53 (3.4)	7 (2.9)	36 (7.2)	136 (8.6)
Dysgeusia	17 (1.1)	3 (1.3)	37 (7.4)	149 (9.4)
Hypoesthesia	19 (1.2)	2 (0.8)	18 (3.6)	58 (3.7)
Disturbance in attention	10 (0.6)	1 (0.4)	10 (2.0)	55 (3.5)
Musculoskeletal and connective tissue disorders	319 (20.4)	48 (20.0)	107 (21.5)	340 (21.5)
Back pain	80 (5.1)	13 (5.4)	28 (5.6)	105 (6.6)
Arthralgia	75 (4.8)	11 (4.6)	23 (4.6)	68 (4.3)
Pain in extremity	44 (2.8)	5 (2.1)	15 (3.0)	48 (3.0)
Muscle spasms	35 (2.2)	7 (2.9)	14 (2.8)	46 (2.9)
Musculoskeletal pain	18 (1.2)	2 (0.8)	15 (3.0)	25 (1.6)
Neck pain	20 (1.3)	3 (1.3)	11 (2.2)	19 (1.2)
Psychiatric disorders	172 (11.0)	34 (14.2)	74 (14.9)	362 (22.9)
Insomnia	74 (4.7)	12 (5.0)	29 (5.8)	148 (9.4)
Depression	35 (2.2)	8 (3.3)	14 (2.8)	68 (4.3)
Anxiety	29 (1.9)	7 (2.9)	9 (1.8)	65 (4.1)

System Organ Class Preferred Term	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
General disorders and administration site conditions	200 (12.8)	32 (13.3)	83 (16.7)	303 (19.2)
Fatigue	67 (4.3)	12 (5.0)	22 (4.4)	93 (5.9)
Irritability	11 (0.7)	4 (1.7)	13 (2.6)	58 (3.7)
Edema peripheral	45 (2.9)	2 (0.8)	6 (1.2)	29 (1.8)
Thirst	11 (0.7)	5 (2.1)	9 (1.8)	31 (2.0)
Chest discomfort	7 (0.4)	5 (2.1)	1 (0.2)	14 (0.9)
Respiratory, thoracic, and mediastinal disorders	193 (12.4)	33 (13.8)	64 (12.9)	254 (16.1)
Cough	54 (3.5)	8 (3.3)	19 (3.8)	76 (4.8)
Sinus congestion	32 (2.0)	6 (2.5)	13 (2.6)	31 (2.0)
Pharyngolaryngeal pain	32 (2.0)	6 (2.5)	6 (1.2)	36 (2.3)
Nasal congestion	22 (1.4)	4 (1.7)	6 (1.2)	31 (2.0)
Asthma	18 (1.2)	3 (1.3)	10 (2.0)	15 (0.9)
Eye disorders	163 (10.4)	32 (13.3)	72 (14.5)	236 (14.9)
Vision blurred	55 (3.5)	15 (6.3)	20 (4.0)	86 (5.4)
Eye pain	22 (1.4)	5 (2.1)	11 (2.2)	35 (2.2)
Dry eye	12 (0.8)	2 (0.8)	7 (1.4)	39 (2.5)
Injury, poisoning, and procedural complications	193 (12.4)	19 (7.9)	77 (15.5)	197 (12.5)
Procedural pain	26 (1.7)	5 (2.1)	12 (2.4)	30 (1.9)
Joint sprain	23 (1.5)	0 (0.0)	10 (2.0)	16 (1.0)
Skin and subcutaneous tissue disorders	145 (9.3)	17 (7.1)	65 (13.1)	244 (15.4)
Rash	34 (2.2)	4 (1.7)	10 (2.0)	41 (2.6)
Alopecia	11 (0.7)	5 (2.1)	13 (2.6)	59 (3.7)
Metabolism and nutrition disorders	121 (7.8)	12 (5.0)	50 (10.0)	158 (10.0)
Hypokalemia	6 (0.4)	1 (0.4)	7 (1.4)	40 (2.5)
Decreased appetite	10 (0.6)	5 (2.1)	9 (1.8)	23 (1.5)
Reproductive system and breast disorders	62 (4.0)	15 (6.3)	25 (5.0)	114 (7.2)
Dysmenorrhea	3 (0.2)	5 (2.1)	2 (0.4)	13 (0.8)
Vascular disorders	91 (5.8)	10 (4.2)	27 (5.4)	76 (4.8)
Hypertension	56 (3.6)	6 (2.5)	14 (2.8)	25 (1.6)
Cardiac disorders	28 (1.8)	4 (1.7)	19 (3.8)	56 (3.5)
Palpitations	12 (0.8)	2 (0.8)	12 (2.4)	27 (1.7)
Immune system disorders	45 (2.9)	5 (2.1)	10 (2.0)	31 (2.0)
Seasonal allergy	35 (2.2)	3 (1.3)	10 (2.0)	27 (1.7)

Treatment-emergent adverse events = adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.4.3 Adverse Events by Maximum Severity

Most TEAEs were mild or moderate in severity for subjects in the 1-Year Cohort. The distributions of TEAEs by maximum severity were similar for the placebo group and QNEXA Mid and Top dose groups **(Table 16)**. In total, 411 (10.6%) subjects had a severe TEAE: 134 (8.6%) subjects in the placebo group, 25 (10.4%) subjects in the QNEXA Low

dose group, 55 (11.0%) subjects in the QNEXA Mid dose group, and 197 (12.5%) subjects in the QNEXA Top dose group.

Table 16. Overview of Adverse Events During the Double-Blind Treatment Period (Safety Set, 1-Year Cohort)

	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Subjects with TEAEs				
Any TEAE	1,186 (76.0)	192 (80.0)	424 (85.1)	1,377 (87.2)
Any drug-related TEAE	433 (27.7)	100 (41.7)	251 (50.4)	920 (58.2)
Maximum severity of TEAEs				
Mild	491 (31.5)	60 (25.0)	151 (30.3)	524 (33.2)
Moderate	561 (35.9)	107 (44.6)	218 (43.8)	656 (41.5)
Severe	134 (8.6)	25 (10.4)	55 (11.0)	197 (12.5)
Deaths	1 (0.1)	0	0	0
Subjects with SAEs				
Any SAE	55 (3.5)	6 (2.5)	15 (3.0)	67 (4.2)
Any treatment-emergent SAE	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)
Any drug-related SAE	6 (0.4)	1 (0.4)	1 (0.2)	8 (0.5)
Study drug discontinuations due to AEs/SAEs				
Any AE	132 (8.5)	28 (11.7)	58 (11.6)	276 (17.5)
Any TEAE	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)
Any drug-related TEAE	82 (5.3)	19 (7.9)	42 (8.4)	210 (13.3)
Any SAE	15 (1.0)	2 (0.8)	4 (0.8)	18 (1.1)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
Treatment-emergent adverse events were defined as adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
AE=adverse event; QNEXA=fixed-dose combination of phentermine and topiramate; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Table 17 summarizes the severe TEAEs that occurred in ≥0.5% of subjects in any treatment group during the double-blind treatment period by preferred term for the 1-Year Cohort.

Table 17. Severe Treatment-Emergent Adverse Events (≥0.5% of Subjects in any Treatment Group) by Preferred Term – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Severe TEAEs	134 (8.6)	25 (10.4)	55 (11.0)	197 (12.5)
Dry mouth	1 (0.1)	1 (0.4)	0 (0.0)	17 (1.1)
Headache	7 (0.4)	1 (0.4)	3 (0.6)	14 (0.9)
Back pain	3 (0.2)	1 (0.4)	3 (0.6)	9 (0.6)
Constipation	2 (0.1)	0 (0.0)	3 (0.6)	9 (0.6)
Nephrolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.6)
Toothache	0 (0.0)	2 (0.8)	1 (0.2)	1 (0.1)
Cholelithiasis	6 (0.4)	2 (0.8)	0 (0.0)	1 (0.1)

Treatment-emergent adverse events = adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.4.4 Targeted Medical Events

Based on the known adverse effects of phentermine HCl and topiramate, as reported in the product labels or literature, and on regulatory questions regarding effects of the drugs on particular systems, certain classes of AEs were specified as TMEs. **Table 18** summarizes targeted medical events that occurred in the 1-Year Cohort.

Table 18. Proportion of Subjects with Treatment-Emergent Adverse Events Categorized as Targeted Medical Events by Class and Subclass – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

TME Class TME Subclass	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Psychiatric disorders class				
Sleep disorders subclass	89 (5.7)	16 (6.7)	34 (6.8)	170 (10.8)
Depression (SMQ) subclass[a]	53 (3.4)	12 (5.0)	19 (3.8)	121 (7.7)
Anxiety subclass	41 (2.6)	11 (4.6)	24 (4.8)	125 (7.9)
Suicide/self-injury (SMQ) subclass	1 (0.1)	1 (0.4)	0	0
Cognitive disorders class				
Attention subclass	10 (0.6)	1 (0.4)	10 (2.0)	56 (3.5)
Memory impairment subclass	10 (0.6)	2 (0.8)	9 (1.8)	40 (2.5)
Language subclass	1 (0.1)	0	3 (0.6)	19 (1.2)
Other cognitive disorders NOS subclass	5 (0.3)	2 (0.8)	5 (1.0)	28 (1.8)
Cardiac disorders class				
Cardiac arrhythmia (SMQ) subclass	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)
Ischemic heart disease (SMQ) subclass	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)
Ophthalmic disorders class				
Ophthalmic disorders subclass	27 (1.7)	6 (2.5)	12 (2.4)	39 (2.5)
Menstrual disorders class				
Menstrual disorders subclass	27 (1.7)	5 (2.1)	8 (1.6)	38 (2.4)
Psychomotor disorders class				
Psychomotor disorders subclass	1 (0.1)	0	2 (0.4)	12 (0.8)

a. The SMQ for depression was modified to exclude adverse events associated with known mechanisms of action for phentermine or topiramate that may have confounded analysis of the given category.
NOS = not otherwise specified; QNEXA = fixed-dose combination of phentermine and topiramate;
SMQ = standardized Medical Dictionary for Regulatory Activities (MedDRA) query; TME = targeted medical event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In the psychiatric disorders class, a dose-related increase in the incidence of TEAEs categorized as anxiety was observed in the 1-Year Cohort. The incidence of TEAEs in the depression subclass was higher in the QNEXA Top dose group than in the other treatment groups. The incidence of TEAEs in the sleep disorders subclass was higher for the treatment groups in the QNEXA Top dose group than in other treatment groups. No subjects in any treatment group had a suicide/self-injury TEAE. Events in this class are further discussed in **Appendix 6**.

In the Cognitive Disorders class, the incidence of TEAEs in the attention and memory impairment subclasses was higher in the QNEXA Mid and Top dose groups than in the QNEXA Low dose and placebo groups. The incidence of TEAEs in the language and other cognitive disorders subclasses was low overall, but higher in the QNEXA Top dose group compared with the other treatment groups. Events in this class are further discussed in **Appendix 6**.

The incidence of TEAEs in the cardiac arrhythmia subclass was higher in the QNEXA Top dose group and QNEXA Mid dose group than in the placebo group. Most of the cardiac arrhythmia TEAEs for the 1-Year Cohort were TEAEs of palpitations, increased heart rate, tachycardia, and syncope. The cardiac arrhythmia TEAEs were primarily mild or moderate in severity and were serious for 4 (0.3%) subjects in the placebo group, 2 (0.4%) subjects in the QNEXA Mid dose group, and 2 (0.1%) subjects in the QNEXA Top dose group. The incidence of TEAEs in the ischemic heart disease subclass was low (0.4% overall) and similar for the treatment groups. No adverse events of valvulopathy were observed. Events in the cardiac arrhythmia and ischemic heart disease subclasses are further discussed in **Section 5.2.3.1** and **5.2.3.2**.

The incidences of TEAEs in the ophthalmic disorders subclass and psychomotor disorders subclass were low overall and higher in the QNEXA groups than in the placebo group. No subjects in any treatment group had a drug abuse/withdrawal TEAE. The incidence of TEAEs in the Psychomotor Disorders class was low overall, but higher in the QNEXA Top dose group compared with the other treatment groups.

3.4.4.1 Severity of Targeted Medical Events

Table 19 summarizes the subclasses of targeted medical events by maximum severity for the 1-Year Cohort. Most of the TEAEs that were categorized as targeted medical events were mild in severity.

Table 19. Treatment-Emergent Targeted Medical Events at the Subclass Level by Maximum Severity – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

TME Subclass Maximum Severity	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Sleep disorders subclass	89 (5.7)	16 (6.7)	34 (6.8)	170 (10.8)
Mild	58 (3.7)	9 (3.8)	19 (3.8)	98 (6.2)
Moderate	29 (1.9)	7 (2.9)	15 (3.0)	65 (4.1)
Severe	2 (0.1)	0 (0.0)	0 (0.0)	7 (0.4)
Depression (SMQ) subclass[a]	53 (3.4)	12 (5.0)	19 (3.8)	121 (7.7)
Mild	24 (1.5)	8 (3.3)	13 (2.6)	67 (4.2)
Moderate	27 (1.7)	3 (1.3)	4 (0.8)	47 (3.0)
Severe	2 (0.1)	1 (0.4)	2 (0.4)	7 (0.4)
Anxiety subclass	41 (2.6)	11 (4.6)	24 (4.8)	125 (7.9)
Mild	23 (1.5)	7 (2.9)	11 (2.2)	68 (4.3)
Moderate	15 (1.0)	2 (0.8)	11 (2.2)	48 (3.0)
Severe	3 (0.2)	2 (0.8)	2 (0.4)	9 (0.6)
Suicide/self-injury (SMQ) subclass	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Attention subclass	10 (0.6)	1 (0.4)	10 (2.0)	56 (3.5)
Mild	5 (0.3)	1 (0.4)	8 (1.6)	37 (2.3)
Moderate	4 (0.3)	0 (0.0)	2 (0.4)	18 (1.1)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Memory impairment subclass	10 (0.6)	2 (0.8)	9 (1.8)	40 (2.5)
Mild	8 (0.5)	2 (0.8)	9 (1.8)	31 (2.0)
Moderate	2 (0.1)	0 (0.0)	0 (0.0)	8 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Language subclass	1 (0.1)	0 (0.0)	3 (0.6)	19 (1.2)
Mild	1 (0.1)	0 (0.0)	2 (0.4)	12 (0.8)
Moderate	0 (0.0)	0 (0.0)	1 (0.2)	6 (0.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Other cognitive disorders NOS subclass	5 (0.3)	2 (0.8)	5 (1.0)	28 (1.8)
Mild	2 (0.1)	0 (0.0)	3 (0.6)	17 (1.1)
Moderate	3 (0.2)	2 (0.8)	1 (0.2)	10 (0.6)
Severe	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Cardiac arrhythmia (SMQ) subclass	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)
Mild	16 (1.0)	1 (0.4)	10 (2.0)	54 (3.4)
Moderate	9 (0.6)	2 (0.8)	9 (1.8)	17 (1.1)
Severe	3 (0.2)	0 (0.0)	2 (0.4)	3 (0.2)
Ischemic heart disease (SMQ) subclass	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)
Mild	2 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Moderate	2 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Severe	4 (0.3)	1 (0.4)	1 (0.2)	3 (0.2)

a. The SMQ for depression was modified to exclude adverse events associated with known mechanisms of action for phentermine or topiramate that may have confounded analysis of the given category.
NOS = not otherwise specified; QNEXA = fixed-dose combination of phentermine and topiramate;
SMQ = standardized Medical Dictionary for Regulatory Activities (MedDRA) query; TME = targeted medical event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.4.5 Serious Adverse Events

Table 20 summarizes treatment-emergent SAEs in the 1-Year Cohort by SOC. The incidence of treatment-emergent SAE was low and similar across the treatment groups. No specific event terms were reported as SAEs by >0.5% of subjects in any treatment group.

Table 20. Treatment-Emergent Serious Adverse Events by System Organ Class – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

System Organ Class Preferred Term	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Any treatment-emergent SAE	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)
Infections and infestations	2 (0.1)	2 (0.8)	3 (0.6)	11 (0.7)
Cardiac disorders	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	8 (0.5)	0 (0.0)	1 (0.2)	6 (0.4)
Hepatobiliary disorders	5 (0.3)	1 (0.4)	0 (0.0)	7 (0.4)
Musculoskeletal and connective tissue disorders	4 (0.3)	0 (0.0)	0 (0.0)	6 (0.4)
Vascular disorders	2 (0.1)	2 (0.8)	1 (0.2)	4 (0.3)
Gastrointestinal disorders	5 (0.3)	0 (0.0)	0 (0.0)	3 (0.2)
General disorders and administration site conditions	7 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Nervous system disorders	4 (0.3)	0 (0.0)	2 (0.4)	2 (0.1)
Respiratory, thoracic, and mediastinal disorders	3 (0.2)	0 (0.0)	2 (0.4)	2 (0.1)
Reproductive system and breast disorders	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)
Renal and urinary disorders	2 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)
Injury, poisoning, and procedural complications	2 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Metabolism and nutrition disorders	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Endocrine disorders	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Treatment-emergent adverse events = adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
QNEXA = fixed-dose combination of phentermine and topiramate; SAE = serious adverse event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.4.6 Discontinuations from Study Drug Due to Adverse Events

Table 21 summarizes the TEAEs that resulted in study drug discontinuation in ≥1% of subjects in any treatment group in the 1-Year Cohort. Overall, 490 (12.6%) subjects in the 1-Year Cohort had a TEAE that resulted in study drug discontinuation. The frequency of these events was generally higher in all QNEXA treatment groups compared with placebo, with the highest incidence occurring in the QNEXA Top dose group.

Table 21. Study Drug Discontinuations Due to Treatment-Emergent Adverse Events Occurring in ≥1% of Subjects in any Treatment Group – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)	QNEXA All Doses (N=2,318) n (%)	Total (N=3,879) n (%)
Discontinuation due to TEAE	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)	359 (15.5)	490 (12.6)
Insomnia	6 (0.4)	0 (0.0)	2 (0.4)	25 (1.6)	27 (1.2)	33 (0.9)
Depression	3 (0.2)	0 (0.0)	4 (0.8)	21 (1.3)	25 (1.1)	28 (0.7)
Paresthesia	0 (0.0)	1 (0.4)	5 (1.0)	18 (1.1)	24 (1.0)	24 (0.6)
Irritability	1 (0.1)	2 (0.8)	4 (0.8)	18 (1.1)	24 (1.0)	25 (0.6)
Anxiety	4 (0.3)	0 (0.0)	1 (0.2)	17 (1.1)	18 (0.8)	22 (0.6)
Dizziness	3 (0.2)	1 (0.4)	6 (1.2)	12 (0.8)	19 (0.8)	22 (0.6)

QNEXA = fixed-dose combination of phentermine and topiramate; TEAE = treatment-emergent adverse event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.5 Clinical Laboratory Evaluations

The clinical laboratory evaluations for the 1-Year Cohort showed no adverse effects of QNEXA treatment on safety laboratory parameters. Overall, no differences were noted between the QNEXA treatment groups and the placebo group in terms of the incidence of serious laboratory-related AEs or study drug discontinuations due to a laboratory-related AE. Three subjects experienced a serious laboratory-related TEAE: one subject in the QNEXA Top dose group had a SAE of abnormal LFT, one subject in the placebo group had a SAE of hypokalemia, and one subject in the placebo group had a SAE of hyponatremia. Eighteen (0.5%) subjects discontinued study drug due to a TEAE in the Investigations SOC: 8 (0.5%) subjects in the placebo group, 2 (0.4%) in the QNEXA Mid dose group, and 8 (0.5%) in the QNEXA Top dose group.

Table 22 shows the mean change in selected laboratory parameters from baseline to endpoint for the 1-Year Cohort. All of the treatment groups had mean decreases in ALT and alkaline phosphatase (ALP) from baseline; the mean decreases in ALT were greater for the QNEXA Mid and Top dose groups than for the QNEXA Low dose and placebo groups. The QNEXA Mid and Top dose groups had mean decreases in AST from baseline, whereas the QNEXA Low dose and placebo groups had mean increases in AST. All QNEXA treatment groups showed mean decreases in serum bicarbonate from baseline; the placebo group had a small mean increase in serum bicarbonate. Other than the mean decreases in ALT and AST for the QNEXA Mid and Top dose groups, no clinically meaningful differences were noted among the treatment groups in mean changes in safety laboratory parameters.

Table 22. Changes from Baseline in Selected Laboratory Parameters – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Parameter Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Alanine transaminase, mU/mL				
n[a]	1,473	230	475	1,525
Baseline[b], mean (SD)	29.4 (15.34)	25.7 (12.99)	31.5 (16.49)	29.8 (15.48)
Endpoint[c], mean (SD)	27.7 (16.88)	23.6 (13.84)	26.3 (14.60)	25.6 (18.48)
Mean change (SD)	-1.7 (14.29)	-2.1 (13.04)	-5.2 (15.92)	-4.2 (19.26)
p-value[d]	<0.0001	0.0134	<0.0001	<0.0001
Aspartate transaminase, mU/mL				
n[a]	1,473	230	475	1,525
Baseline[b], mean (SD)	23.8 (8.78)	21.4 (7.37)	25.1 (9.23)	24.1 (8.65)
Endpoint[c], mean (SD)	24.2 (12.00)	23.3 (35.38)	23.8 (18.04)	22.6 (9.41)
Mean change (SD)	0.4 (10.78)	1.9 (35.56)	-1.3 (17.83)	-1.5 (10.20)
p-value[d]	0.1953	0.4165	0.1159	<0.0001
Creatinine, mg/dL				
n[a]	1,475	230	475	1,525
Baseline[b], mean (SD)	0.86 (0.174)	0.84 (0.156)	0.86 (0.177)	0.85 (0.170)
Endpoint[c], mean (SD)	0.84 (0.176)	0.84 (0.165)	0.89 (0.188)	0.89 (0.183)
Mean change (SD)	-0.02 (0.101)	0.00 (0.094)	0.03 (0.104)	0.04 (0.111)
p-value[d]	<0.0001	0.9944	<0.0001	<0.0001
Alkaline phosphatase, mU/mL				
n[a]	1,475	230	475	1,525
Baseline[b], mean (SD)	79.8 (22.27)	79.7 (20.59)	78.7 (20.71)	79.0 (20.96)
Endpoint[c], mean (SD)	77.6 (22.21)	78.0 (20.90)	76.1 (21.78)	76.5 (21.79)
Mean change (SD)	-2.2 (12.49)	-1.7 (12.01)	-2.6 (13.97)	-2.5 (12.97)
p-value[d]	<0.0001	0.0295	<0.0001	<0.0001
Total bilirubin, mg/dL				
n[a]	1,475	230	475	1,525
Baseline[b], mean (SD)	0.45 (0.197)	0.43 (0.216)	0.46 (0.208)	0.45 (0.204)
Endpoint[c], mean (SD)	0.48 (0.210)	0.48 (0.215)	0.49 (0.226)	0.48 (0.211)
Mean change (SD)	0.03 (0.161)	0.05 (0.143)	0.03 (0.176)	0.03 (0.169)
p-value[d]	<0.0001	<0.0001	<0.0001	<0.0001
Bicarbonate, mEq/L				
n[a]	1,475	230	475	1,525
Baseline[b], mean (SD)	26.2 (2.52)	26.4 (2.54)	26.1 (2.72)	26.3 (2.49)
Endpoint[c], mean (SD)	26.4 (2.77)	24.9 (2.56)	25.8 (2.91)	25.0 (2.96)
Mean change (SD)	0.2 (3.09)	-1.6 (3.01)	-0.3 (3.12)	-1.3 (3.19)
p-value[d]	0.0152	<0.0001	0.0605	<0.0001
Potassium, mEq/L				
n[a]	1,474	230	475	1,523
Baseline[b], mean (SD)	4.28 (0.386)	4.27 (0.357)	4.26 (0.396)	4.27 (0.390)
Endpoint[c], mean (SD)	4.37 (0.409)	4.33 (0.382)	4.27 (0.415)	4.27 (0.434)
Mean change (SD)	0.09 (0.416)	0.07 (0.378)	0.02 (0.414)	0.01 (0.456)
p-value[d]	<0.0001	0.0077	0.3245	0.6410

Table 22. Changes from Baseline in Selected Laboratory Parameters – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort) (cont'd)

Parameter Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Blood urea nitrogen, mg/dL				
n[a]	1,475	230	475	1,525
Baseline[b], mean (SD)	14.2 (4.12)	13.0 (3.47)	14.8 (4.04)	14.1 (3.82)
Endpoint[c], mean (SD)	14.3 (4.43)	13.1 (3.75)	15.9 (4.61)	15.0 (4.40)
Mean change (SD)	0.2 (3.63)	0.1 (3.42)	1.2 (4.04)	0.8 (3.64)
p-value[d]	0.1183	0.5373	<0.0001	<0.0001
Hemoglobin, g/dL				
n[a]	1,212	195	442	1,392
Baseline[b], mean (SD)	14.0 (1.32)	13.9 (1.20)	14.1 (1.33)	14.0 (1.25)
Endpoint[c], mean (SD)	13.8 (1.34)	13.9 (1.24)	14.0 (1.38)	13.8 (1.33)
Mean change (SD)	-0.2 (0.75)	0.0 (0.75)	-0.1 (0.76)	-0.1 (0.80)
p-value[d]	<0.0001	0.5407	0.0005	<0.0001
Hematocrit, %				
n[a]	1,212	195	442	1,392
Baseline[b], mean (SD)	41.6 (3.70)	41.1 (3.35)	42.0 (3.74)	41.4 (3.54)
Endpoint[c], mean (SD)	41.2 (3.76)	41.2 (3.62)	41.6 (3.87)	41.2 (3.78)
Mean change (SD)	-0.4 (2.36)	0.1 (2.24)	-0.4 (2.40)	-0.3 (2.51)
p-value[d]	<0.0001	0.5239	0.0010	<0.0001

a. n is the number of subjects with baseline and endpoint measurements.
b. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
c. Endpoint is the last available measurement obtained during the double-blind treatment period.
d. Two-sided p-value is from t-test testing whether change is equal to 0 within the treatment group.
QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Table 23 summarizes the incidence of elevations in liver function tests during the double-blind treatment period for the 1-Year Cohort based on categories as specified in the FDA Guidance entitled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (FDA Guidance 2009). The rates of significant elevations in liver function tests were low and similar across the treatment groups. No differences were observed relative to placebo in any QNEXA treatment groups.

Table 23. Significant Elevations in Liver Function Tests during Double-Blind Treatment – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Liver Function Test Category	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
ALT elevation				
>3 × ULN	15 (1.0)	2 (0.8)	3 (0.6)	16 (1.0)
>5 × ULN	5 (0.3)	0 (0.0)	1 (0.2)	6 (0.4)
>10 × ULN	1 (0.1)	0 (0.0)	1 (0.2)	3 (0.2)
>20 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST elevation				
>3 × ULN	12 (0.8)	2 (0.8)	2 (0.4)	5 (0.3)
>5 × ULN	4 (0.3)	2 (0.8)	2 (0.4)	3 (0.2)
>10 × ULN	1 (0.1)	1 (0.4)	1 (0.2)	1 (0.1)
>20 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total bilirubin elevation				
>1.5 × ULN	12 (0.8)	2 (0.8)	4 (0.8)	12 (0.8)
>2 × ULN	3 (0.2)	1 (0.4)	0 (0.0)	1 (0.1)
Alkaline phosphatase elevation				
>1.5 × ULN	10 (0.6)	0 (0.0)	2 (0.4)	5 (0.3)
ALT or AST with total bilirubin elevation				
ALT or AST >3 × ULN and total bilirubin >1.5 × ULN	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)
ALT or AST >3 × ULN and total bilirubin >2 × ULN	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)

All measurements taken during the double-blind treatment period are considered.
ALT = alanine transaminase; AST = aspartate transaminase;
QNEXA = fixed-dose combination of phentermine and topiramate; ULN = upper limit of normal.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In the 1-Year Cohort, two subjects had elevations in liver transaminases of >3 × upper limit of normal (ULN) AST or ALT plus >2 × ULN total bilirubin. In both of these subjects, elevations in transaminases occurred concurrently with SAEs of cholelithiasis, which resolved with treatment. These two events are described below:

- One subject who received placebo in study OB-302 was hospitalized with severe right upper quadrant abdominal pain associated with nausea, fever, and chills. Laboratory test results upon admission showed AP 234 IU/L, total bilirubin 4.8 mg/dL, ALT 232 IU/L, AST 88 IU/L, and white blood cell 17 K/µL. An abdominal ultrasound revealed no gallstones, minimal sludge, thickened gallbladder wall, mild hepatomegaly, and mild splenomegaly. An endoscopic procedure showed mildly dilated common bile duct, and the cystic duct was filled with stones. Biopsy results of the gallbladder revealed a diagnosis of chronic cholecystitis with acute exacerbation and eosinophils. The subject was treated for this event, and he recovered from the event 2 days later and was discharged from the hospital.

- One subject who received QNEXA Top dose in study OB-202 was hospitalized with cholelithiasis. After 4 months on study, the subject complained of bloating, pressure, and feelings of hunger that did not resolve with eating. Laboratory values showed white blood cell count of 12.7 K/µL, lipase 2203 IU/L, total bilirubin 2.9 mg/dL, AST 494 IU/L, and ALT 357 IU/L, all of which were elevated. An abdominal ultrasound revealed intra and extrahepatic biliary and pancreatic duct dilation, numerous gallstones and sludge and a hypoechoic pancreas. An endoscopic retrograde cholangiopancreatography and cholecystectomy were performed. The subject was treated for this event, and she recovered from the event on the same day and was discharged from the hospital. The investigator assessed the worsening cholelithiasis as moderate in severity and as not related to study medication.

Both subjects remained on study drug, and the events resolved with no sequelae.

Table 24 provides a summary of changes in serum bicarbonate, serum potassium, and serum creatinine during the double-blind treatment period for the 1-Year Cohort. The percentage of subjects with serum bicarbonate values <17 mEq/L at any time point during the double-blind treatment period was higher in the QNEXA treatment groups than in the placebo group, although no dose-related trend was evident. No subjects in the placebo or QNEXA Low dose groups and few subjects in the QNEXA Mid and Top dose groups had serum potassium <3.0 mmol/L concurrent with a decrease of >0.5 mmol/L from baseline. Similarly, no subjects in the placebo, QNEXA Low dose, or QNEXA Mid dose groups, and not more than 2 (0.1%) subjects in the QNEXA Top dose group had increased serum creatinine >100% of baseline at the final visit, during the titration phase, or during the maintenance phase.

Table 24. Changes in Selected Laboratory Parameters during the Double-Blind Treatment Period – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Change in Chemistry Parameter Time Point	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Serum bicarbonate <17 mEq/L				
At final visit	1 (0.1)	2 (0.8)	0	7 (0.4)
During titration phase	1 (0.1)	0	3 (0.6)	12 (0.8)
During maintenance phase	3 (0.2)	4 (1.7)	6 (1.2)	23 (1.5)
Persistence	1 (0.1)	2 (0.8)	1 (0.2)	11 (0.7)
Serum potassium <3.0 mmol/L and decrease from baseline >0.5 mmol/L				
At final visit	0	0	0	2 (0.1)
During titration phase	0	0	1 (0.2)	4 (0.3)
During maintenance phase	0	0	1 (0.2)	7 (0.4)
Persistence	0	0	1 (0.2)	2 (0.1)
Serum creatinine increase >100% from baseline				
At final visit	0	0	0	1 (0.1)
During titration phase	0	0	0	2 (0.1)
During maintenance phase	0	0	0	1 (0.1)
Persistence	0	0	0	1 (0.1)

All measurements taken during the double-blind treatment period are considered.
The titration phase is the period of time from the first dose of double-blind study drug up to and including the Week 4 visit date. For subjects continuing beyond Week 4, the Week 4 visit date is the cutoff. The maintenance phase is defined as the period of time from the Week 4 visit date to the date of completion or early termination from the study.
Persistence is defined as occurring at two consecutive visits or being present at the final visit.
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

3.6 Summary of Safety

The integrated analysis of safety was based on 3879 subjects enrolled in the three pivotal Phase 3 studies (OB-301, OB-302, and OB-303) and two supportive Phase 2 studies (OB-202 and DM-230). The safety population was diverse in age, race, and sex, representing the broader population of obese and overweight subjects with multiple comorbidities, including depression. Most side effects were mild to moderate in severity, manageable and reversible, and consistent with the known safety profile of phentermine HCl and topiramate. No unexpected toxicity was observed. The integrated safety analysis demonstrated that QNEXA is safe and generally well tolerated in the intended population over a period of 1 year at all tested dose levels. There was no suicidal behavior reported in the QNEXA clinical program. In the majority of subjects, there were no clinically meaningful effects on cognitive function, anxiety, or depression. There were no serious adverse events reported in the 1-Year Cohort. Reported psychiatric and cognitive effects were primarily mild, manageable, and reversible with cessation of therapy. There was no clinically meaningful effect on cardiovascular function over 1 year.

Most TEAEs were observed during the first few months on study, and no new safety signals or substantially increased frequency of TEAEs emerged with continued therapy. The most

frequently reported TEAEs associated with QNEXA were paresthesia, dry mouth, constipation, upper respiratory tract infection, nasopharyngitis, headache, and dysgeusia. The incidences of paresthesia, dry mouth, constipation, dysgeusia, insomnia, dizziness, hypoesthesia, irritability, alopecia, dry eye, and hypokalemia were higher in the QNEXA groups than in the placebo group and increased in a dose-related manner. However, few subjects discontinued study drug due to these AEs. In fact, most subjects who experienced a TEAE continued study treatment, and the overall discontinuation rate for any reason was higher in the placebo group than in the QNEXA groups. Overall, the rate of discontinuation from study drug in the QNEXA groups was low and dose-related.

The incidence of SAEs in the 1-Year Cohort was low and similar across the treatment groups. In particular, the incidence of cardiac SAEs was not increased in the QNEXA groups compared with placebo groups. Only 1 death occurred during the studies, in a placebo-treated subject who died from cardiopulmonary arrest during the first 6 months in study OB-303.

4 EXTENDED SAFETY AND EFFICACY DATA: 2-YEAR COHORT

4.1 OB-305: Study Design

Study OB-305, a non-randomized, double-blind, placebo-controlled, 1-year extension to study OB-303 collected additional long-term safety and efficacy data on QNEXA Mid dose and Top dose during a second year of exposure of obese subjects with obesity-related comorbidities. This study was not part of the original 2009 QNEXA NDA submission or the 2010 QNEXA EMDAC meeting. The study was recently published **(Appendix 3)**.

Study OB-305 was designed to assess the impact of weight loss and maintenance of weight loss on metabolic and cardiovascular comorbidities, particularly the progression to type 2 diabetes. Subjects who elected to enroll in this extension study continued on the same double-blind treatment they were randomized to in study OB-303 for up to 52 weeks of additional exposure. The primary efficacy endpoints were percent weight loss from study OB-303 baseline to Week 108 and percentage of subjects with at least 5% weight loss from study OB-303 baseline. Percent weight loss was analyzed using an ANCOVA model with treatment, gender, and diabetic status as factors and baseline weight as a covariate.

Secondary endpoints included:

- Absolute weight loss from study OB-303 baseline to Week 108;
- Proportion of subjects achieving reductions in total body weight from study OB-303 baseline of at least 10%, 15% and 20% at Week 108; and
- Change from study OB-303 baseline in waist circumference at Week 108.

Additional endpoints included measures of percent weight loss, absolute weight loss, waist circumference, change from study OB-303 baseline in LDL-C, HDL-C, TC, TG, HbA_{1c}, fasting glucose, fasting insulin, SBP, DBP, and time to onset of type 2 diabetes.

Logistic regression with treatment, gender, and diabetic status as factors, and baseline weight as a covariate was used to compare the percentage of subjects achieving categorical weight reductions. Change in waist circumference and obesity-associated risk factors were analyzed using the same ANCOVA model specified for percent weight loss. No adjustments were made for multiple comparisons.

4.1.1 OB-305: Study Population

The study population included adult subjects from study sites with high enrollment and retention who completed study OB-303 on treatment with a body mass index (BMI) ≥22 kg/m^2 and who had not developed a condition that would contraindicate the administration of study drug or prevent continued compliance with protocol requirements. Site selection for study OB-305 was based on enrollment and completion numbers from study OB-303.

Most subjects were female (66.4%) and Caucasian (85.3%). The mean age of subjects was 51.9 years. At baseline (start of study OB-303), mean weight was 101.7 kg, mean BMI was 36.1 kg/m^2, and mean waist circumference was 112.6 cm, mean systolic blood pressure (SBP) was 127.8 mmHg, mean diastolic blood pressure (DBP) was 80.0 mmHg, and mean heart rate was 72.0 bpm. At baseline, mean low-density lipoprotein cholesterol (LDL-C) was 122.1 mg/dL, mean high-density lipoprotein cholesterol (HDL-C) was 49.0 mg/dL, mean total cholesterol (TC) was 202.4 mg/dL, and mean triglycerides (TG) was 156.6 mg/dL. In total, 145 (21.5%) subjects had diabetes at the start of study OB-305. With the exception of diabetic status and heart rate, the treatment groups were comparable with respect to demographic and baseline characteristics. **Appendix 2** provides a summary of demographic and baseline characteristics of subjects enrolled in study OB-305.

A total of 676 subjects enrolled in the study. In total, 574 (84.9%) completed all study visits and 102 (15.1%) subjects discontinued from the study (**Table 25**). The percentages of subjects who completed the study were 86.8% in the placebo group, 83.8% in the QNEXA Mid dose group, and 84.1% in the QNEXA Top dose group. Of the 676 enrolled subjects, 568 (84.0%) subjects completed all study visits on study drug. The percentages of subjects who completed the study on study drug were 86.3% in the placebo group, 82.5% in the QNEXA Mid dose group, and 83.1% in the QNEXA Top dose group.

Table 25. Subject Disposition – Study OB-305

	Placebo (N=227) n	QNEXA Mid (N=154) n	QNEXA Top (N=295) n
Completed study	197	129	248
Completed study on study drug	196	127	245
Discontinued study drug			
Lost to follow-up	4	4	20
Adverse event	7	7	13
Withdrew consent	7	9	11
Lack of efficacy	3	1	0

QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

4.2 Efficacy (2-Year Cohort)

Efficacy results are presented in the same order as for the pivotal program for ease of reference with use of nominal p-values for secondary and exploratory endpoints.

4.2.1 Primary Endpoint and Other Measures of Weight Loss at Two Years

4.2.1.1 Percent Weight Loss

Results from study OB-305 demonstrate that significant weight loss with QNEXA is maintained after two years of treatment. In study OB-305, LS mean weight losses of 10.5% and 9.3% were achieved at Week 108 with QNEXA Top dose and QNEXA Mid dose, respectively, compared to 1.8% with placebo. At the Week 108 time point, the dose-related effects of QNEXA were still observed, with QNEXA Top dose and QNEXA Mid dose resulting in significantly greater percent weight loss than placebo.

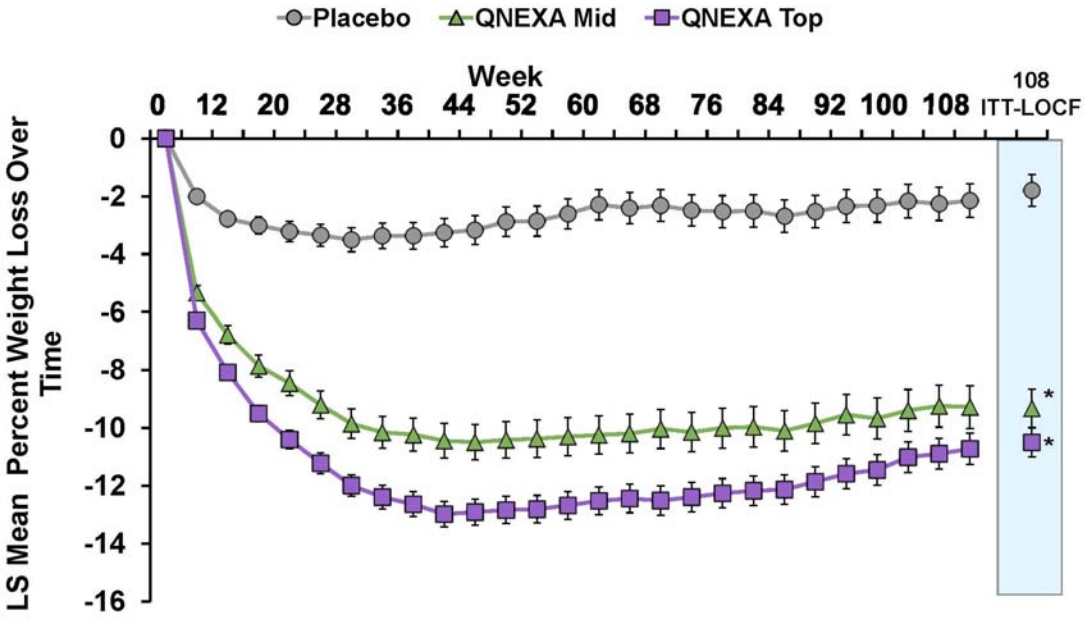
Table 26 presents the results for percent weight loss at the final study visit. In study OB-305 mean percent weight loss continued to remain relatively stable until Week 72 and then progressively decreased from Week 72 to the end of the study for the QNEXA Top dose group. For the QNEXA Mid dose group, mean percent weight loss continued to remain relatively stable until Week 84 and then plateaued from Week 84 to the end of the study. For the placebo group, a slight upward trend from the treatment nadir at Week 28 continued to the end of the study. **Figure 22** shows mean percent weight loss over two years of treatment in study OB-305.

Table 26. Percent Weight Loss at Study Endpoint – Study OB-305 (ITT-LOCF)

Treatment	Percent Weight Loss at Week 108[a]		
	N	LS Mean (SE)	p-value
Placebo	227	1.8 (0.55)	--
QNEXA Mid	153	9.3 (0.67)	<0.0001
QNEXA Top	295	10.5 (0.50)	<0.0001

[a] Week 108 with LOCF is the last available weight measurement during the double-blind treatment period in study OB-305
LS mean, SE, and two-sided p-value are from ANCOVA model with treatment, gender, and diabetic status as fixed effects and baseline as a covariate. Two-sided p-value is for treatment comparison of QNEXA with placebo.
ITT-LOCF = intent-to-treat–last observation carried forward; LS = least squares;
QNEXA = fixed-dose combination of phentermine and topiramate; SE = standard error.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Figure 22. Percent Weight Loss from Baseline Over Time – Study OB-305 (Completer Population and ITT-LOCF Set)



*p<0.001 versus placebo.
Week 0 is defined as the last measurement obtained on or before the first dose date of double-blind study drug in Study OB-303.
Completer Population = all observed data for subjects still on drug at the reported time point;
ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

4.2.1.2 Weight Loss by Benchmark Category

Results of categorical weight loss were also maintained through year two in study OB-305 (**Table 27**).

Table 27. Percentage of Subjects with ≥5%, ≥10%, and ≥15% Weight Loss at Study Endpoint – Study OB-305 (ITT-LOCF[a] Set)

Analysis Category	Placebo N=227	QNEXA Mid N=153	QNEXA Top N=295
≥5% weight loss	30.0	75.2*	79.3*
≥10% weight loss	11.5	50.3*	53.9*
≥15% weight loss	6.6	24.2*	31.9*

a. The ITT-LOCF analysis includes the last post-dose measurement for all subjects in the ITT set, regardless of whether or not the subject was on study drug.
*p<0.001 versus placebo.
†p<0.05 versus placebo.
‡p<0.01 versus QNEXA Low (OB-302) or QNEXA Mid (OB-303).
ITT-LOCF = intent-to-treat–last observation carried forward;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

4.2.2 Secondary and Exploratory Endpoints

In study OB-305, the reduction from baseline in waist circumference was significantly greater in the QNEXA Top dose group (-10.6 cm) and the QNEXA Mid dose group (-9.8 cm) compared with the placebo group (-3.6 cm) at Week 108 ($p<0.0001$ versus placebo, in each case).

In study OB-305, significant mean decreases in SBP and DBP were observed in each treatment group after two years of treatment compared to baseline, and improvements observed in the first year of treatment were maintained. The differences between QNEXA and placebo were not statistically significant, however. Consistent with study OB-303, the percentage of subjects who had an increase in the number of concomitant antihypertensive medications during the 2-year treatment period was higher in the placebo group than in the QNEXA groups and the percentage of subjects with a decrease in the number of concomitant antihypertensive medications was higher in the QNEXA groups than in the placebo group. These changes in medications may have contributed to the lack of statistically significant differences in SBP and DBP between QNEXA and placebo.

In subjects treated with QNEXA Top dose, TG, and HDL-C levels were significantly different from subjects treated with placebo in study OB-305. In study OB-305, treatment with Mid dose and Top dose QNEXA resulted in decreases in HbA_{1c}, and treatment with Top dose QNEXA resulted in decreases in fasting serum glucose relative to placebo.

Table 28 presents the annualized incidence rate of type 2 diabetes based on laboratory thresholds (fasting glucose ≥126 mg/dL or 2-hour OGTT glucose ≥200 mg/dL) for subjects in study OB-305 without type 2 diabetes at the time of entry into study OB-303. While the number of subjects is too small to reach any conclusions, the results are consistent with the 1-year data. Clinically meaningful and significant improvements in fasting insulin, OGTT glucose and insulin excursions, and insulin resistance were observed with QNEXA treatment relative to placebo after two years of treatment. The incidence of new onset diabetes was lower in the QNEXA groups (QNEXA Top dose, 0.9%; QNEXA Mid dose, 1.7%) than in the placebo group (3.7%).

Table 28. Annualized Incidence Rate of Type 2 Diabetes Based on Consecutive Laboratory Thresholds – Study OB-305 (ITT-LOCF) Subjects without Type 2 Diabetes at the Time of Entry into Study OB-303

	Placebo (N=171)	QNEXA Mid (N=125)	QNEXA Top (N=229)
n (%)[a]	12 (7.0)	4 (3.2)	4 (1.7)
Subject-years of follow up[b]	326.6	242.4	455.5
Annualized incidence rate[c]	3.7	1.7	0.9
Relative Risk[d]			
Estimate	--	0.46	0.25
95% CI	--	(0.15 , 1.38)	(0.08 , 0.76)

Note: Five subjects did not have diabetes at the time of entry into Study OB-303 but did have onset on or before the first dose date of study drug in Study OB-303 and have been excluded from this analysis.
a. n is the number of subjects newly diagnosed with type 2 diabetes based on consecutive measurements of fasting glucose ≥126 mg/dL or OGTT glucose ≥200 mg/dL.
b. Subject-years of follow up is calculated as the sum across all subjects of the number of days from the randomization date in Study OB-303 to the date of onset of type 2 diabetes (or censoring time if the subject did not develop type 2 diabetes) divided by 365.25. The date of onset is the date of the first occurrence of consecutive post-baseline measurements of fasting glucose ≥126 mg/dL or OGTT glucose ≥200 mg/dL. Censoring time is calculated as the number of days from the randomization date in Study OB-303 to the completion or early termination date from Study OB-305.
c. Annualized incidence rate per 100 subject years is calculated as 100 × number of newly diagnosed subjects/ subject-years of follow up.
d. Relative risk is calculated as QNEXA vs. placebo.
CI = confidence interval; OGTT = oral glucose tolerance testing;
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

4.3 Safety (2-Year Cohort)

Safety data from all subjects who entered study OB-305 are presented in the 2-Year Cohort. Data that summarize the 2-year treatment period (OB-303 and OB-305) are presented.

4.3.1 Extent of Exposure

Overall mean exposure to study drug for the 2-Year Cohort was 728.5 days, and overall median exposure to study drug was 756.0 days. The exposure to study drug was similar for each treatment group. The majority of subjects in each treatment group had more than 104 weeks of exposure to study drug.

Table 29 summarizes extent of exposure to study drug for the 2-Year Cohort.

Table 29. Cumulative Extent of Exposure to Study Drug (Safety Set – 2-Year Cohort)

	Placebo (N=227)	QNEXA Mid (N=153)	QNEXA Top (N=295)	Total (N=675)
Extent of exposure (days)				
Mean (SD)	733.4 (75.22)	724.4 (92.31)	726.9 (85.88)	728.5 (83.96)
Median	757.0	757.0	756.0	756.0
Number (%) in specified exposure range				
56 weeks to ≤108 weeks	112 (49.3)	74 (48.4)	164 (55.6)	350 (51.9)
>108 weeks	115 (50.7)	79 (51.6)	131 (44.4)	325 (48.1)

QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

4.3.2 Subject Disposition

Table 30 summarizes subject disposition for the 2-Year Cohort. Of the 676 enrolled subjects, 574 (84.9%) subjects completed all study visits and 102 (15.1%) subjects discontinued from the study. A similar percentage of subjects in each treatment group completed the study (placebo, 86.8%; QNEXA Mid 83.8%; and QNEXA Top 84.1%). The most common reasons for discontinuation from the study were withdrawal of consent (4.7%), loss to follow-up (4.4%), and adverse event (2.5%).

Table 30. Subject Disposition – (Safety Set, 2-Year Cohort)

	Placebo (N=227) n (%)	QNEXA Mid (N=154) n (%)	QNEXA Top (N=295) n (%)	Total (N=676) n (%)
Eligible subjects who elected not to enroll in study OB-305[a]	100	40	50	190
Enrolled in study OB-305[b]	227 (100.0)	154 (100.0)	295 (100.0)	676 (100.0)
Completed all study visits	197 (86.8)	129 (83.8)	248 (84.1)	574 (84.9)
Discontinued from study OB-305	30 (13.2)	25 (16.2)	47 (15.9)	102 (15.1)
Subject withdrew consent	9 (4.0)	11 (7.1)	12 (4.1)	32 (4.7)
Subject lost to follow-up	5 (2.2)	4 (2.6)	21 (7.1)	30 (4.4)
Adverse event	6 (2.6)	4 (2.6)	7 (2.4)	17 (2.5)
Protocol non-compliance	3 (1.3)	1 (0.6)	1 (0.3)	5 (0.7)
Requirement for restricted medication	2 (0.9)	0 (0.0)	2 (0.7)	4 (0.6)
Lack of efficacy	2 (0.9)	1 (0.6)	0 (0.0)	3 (0.4)
Pregnancy	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.3)
Other	2 (0.9)	4 (2.6)	3 (1.0)	9 (1.3)
Completed all visits on study drug	196 (86.3)	127 (82.5)	245 (83.1)	568 (84.0)
Discontinued study drug	31 (13.7)	26 (16.9)	50 (16.9)	107 (15.8)
Subject lost to follow-up	4 (1.8)	4 (2.6)	20 (6.8)	28 (4.1)
Adverse event	7 (3.1)	7 (4.5)	13 (4.4)	27 (4.0)
Subject withdrew consent	7 (3.1)	9 (5.8)	11 (3.7)	27 (4.0)
Protocol non-compliance	3 (1.3)	1 (0.6)	1 (0.3)	5 (0.7)
Lack of efficacy	3 (1.3)	1 (0.6)	0 (0.0)	4 (0.6)
Requirement for restricted medication	2 (0.9)	0 (0.0)	1 (0.3)	3 (0.4)
Pregnancy	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.3)
Other	4 (1.8)	4 (2.6)	3 (1.0)	11 (1.6)
Safety Set	227 (100.0)	153 (99.4)	295 (100.0)	675 (99.9)
Intent-to-Treat Set	227 (100.0)	153 (99.4)	295 (100.0)	675 (99.9)

QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

4.3.3 Adverse Events

4.3.3.1 Overview of Adverse Events

No important differences were observed between the 1-Year and 2-Year Cohorts in the types of TEAEs or incidence of specific TEAEs with QNEXA treatment, indicating that long-term treatment did not result in any new types of AEs or increased rates of AEs.

Table 31 provides an overall summary of AEs during studies OB-303 and OB-305 for the 2-Year Cohort. A total of 637 (94.4%) subjects had a TEAE, 319 (47.3%) subjects had a TEAE that was considered by the investigators to be related to study drug. The incidence of drug-related TEAEs was higher in the QNEXA treatment groups than the placebo group. Most of the TEAEs and drug-related TEAEs were mild or moderate in severity. A higher

percentage of subjects in the QNEXA Top dose group than in the placebo group and QNEXA Mid dose group had a TEAE that was severe in severity.

Table 31. Overview of Adverse Event (Safety Set, 2-Year Cohort)

	Placebo (N=227) n (%)	QNEXA Mid (N=153) n (%)	QNEXA Top (N=295) n (%)	Total (N=675) n (%)
Subjects with TEAEs				
Any TEAE	218 (96.0)	142 (92.8)	277 (93.9)	637 (94.4)
Any drug-related TEAE	68 (30.0)	74 (48.4)	177 (60.0)	319 (47.3)
Maximum severity of TEAEs				
Mild	72 (31.7)	47 (30.7)	106 (35.9)	225 (33.3)
Moderate	115 (50.7)	75 (49.0)	117 (39.7)	307 (45.5)
Severe	31 (13.7)	20 (13.1)	54 (18.3)	105 (15.6)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with treatment-emergent SAEs				
Any SAE	14 (6.2)	9 (5.9)	24 (8.1)	47 (7.0)
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study drug discontinuations due to adverse events				
Any TEAE	7 (3.1)	7 (4.6)	13 (4.4)	27 (4.0)
Any drug-related TEAE	1 (0.4)	2 (1.3)	8 (2.7)	11 (1.6)
Any SAE	4 (1.8)	3 (2.0)	0 (0.0)	7 (1.0)

Treatment-emergent adverse events were defined as adverse events that started on or after the first dose of double-blind study drug in study OB-303 and up to 28 days after the last dose of study drug in Study OB-305.
QNEXA = fixed-dose combination of phentermine and topiramate; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

4.3.3.2 Common Adverse Events

Table 32 summarizes the most common TEAEs (experienced by ≥2% of subjects in any treatment group) during study OB-305 (second year only) by system organ class and preferred term. The incidences of the following TEAEs (preferred terms) were higher in the QNEXA groups than in the placebo group: influenza, back pain, constipation, diarrhea, procedural pain, paraesthesia, depression, and abdominal bruit.

Table 32. Summary of Treatment-Emergent Adverse Events (≥2% of Subjects in Any Treatment Group) by System Organ Class and Preferred Term – Study OB-305 (Safety Set, 2-Year Cohort)

System Organ Class Preferred Term	Placebo (N=227) n (%)	QNEXA Mid (N=153) n (%)	QNEXA Top (N=295) n (%)	Total (N=675) n (%)
Infections and infestations	117 (51.5)	82 (53.6)	140 (47.5)	339 (50.2)
Upper respiratory tract infection	42 (18.5)	26 (17.0)	45 (15.3)	113 (16.7)
Nasopharyngitis	26 (11.5)	13 (8.5)	26 (8.8)	65 (9.6)
Sinusitis	18 (7.9)	12 (7.8)	28 (9.5)	58 (8.6)
Urinary tract infection	13 (5.7)	14 (9.2)	18 (6.1)	45 (6.7)
Influenza	8 (3.5)	10 (6.5)	19 (6.4)	37 (5.5)
Bronchitis	7 (3.1)	8 (5.2)	10 (3.4)	25 (3.7)
Gastroenteritis	6 (2.6)	2 (1.3)	9 (3.1)	17 (2.5)
Gastroenteritis viral	6 (2.6)	4 (2.6)	4 (1.4)	14 (2.1)
Ear infection	2 (0.9)	3 (2.0)	7 (2.4)	12 (1.8)
Tooth abscess	4 (1.8)	4 (2.6)	4 (1.4)	12 (1.8)
Pneumonia	4 (1.8)	4 (2.6)	3 (1.0)	11 (1.6)
Viral infection	3 (1.3)	2 (1.3)	6 (2.0)	11 (1.6)
Tooth infection	1 (0.4)	3 (2.0)	4 (1.4)	8 (1.2)
Oral herpes	2 (0.9)	3 (2.0)	2 (0.7)	7 (1.0)
Musculoskeletal and connective tissue disorders	52 (22.9)	39 (25.5)	71 (24.1)	162 (24.0)
Arthralgia	14 (6.2)	7 (4.6)	16 (5.4)	37 (5.5)
Back pain	7 (3.1)	9 (5.9)	15 (5.1)	31 (4.6)
Musculoskeletal pain	11 (4.8)	4 (2.6)	6 (2.0)	21 (3.1)
Pain in extremity	11 (4.8)	3 (2.0)	5 (1.7)	19 (2.8)
Osteoarthritis	5 (2.2)	4 (2.6)	7 (2.4)	16 (2.4)
Muscle spasms	5 (2.2)	4 (2.6)	6 (2.0)	15 (2.2)
Myalgia	2 (0.9)	3 (2.0)	6 (2.0)	11 (1.6)
Gastrointestinal disorders	40 (17.6)	34 (22.2)	65 (22.0)	139 (20.6)
Constipation	7 (3.1)	11 (7.2)	12 (4.1)	30 (4.4)
Nausea	4 (1.8)	10 (6.5)	4 (1.4)	18 (2.7)
Diarrhea	3 (1.3)	3 (2.0)	11 (3.7)	17 (2.5)
Toothache	5 (2.2)	4 (2.6)	2 (0.7)	11 (1.6)
Abdominal pain	5 (2.2)	0 (0.0)	3 (1.0)	8 (1.2)
Hemorrhoids	1 (0.4)	1 (0.7)	6 (2.0)	8 (1.2)
Vomiting	2 (0.9)	4 (2.6)	1 (0.3)	7 (1.0)
Abdominal discomfort	0 (0.0)	3 (2.0)	0 (0.0)	3 (0.4)
Injury, poisoning, and procedural complications	35 (15.4)	30 (19.6)	66 (22.4)	131 (19.4)
Procedural pain	4 (1.8)	8 (5.2)	14 (4.7)	26 (3.9)
Joint sprain	4 (1.8)	5 (3.3)	7 (2.4)	16 (2.4)
Muscle strain	4 (1.8)	6 (3.9)	6 (2.0)	16 (2.4)
Contusion	2 (0.9)	3 (2.0)	7 (2.4)	12 (1.8)
Respiratory, thoracic, and mediastinal disorders	29 (12.8)	20 (13.1)	34 (11.5)	83 (12.3)
Cough	4 (1.8)	4 (2.6)	10 (3.4)	18 (2.7)
Pharyngolaryngeal pain	6 (2.6)	3 (2.0)	8 (2.7)	17 (2.5)
Sinus congestion	6 (2.6)	4 (2.6)	3 (1.0)	13 (1.9)

System Organ Class Preferred Term	Placebo (N=227) n (%)	QNEXA Mid (N=153) n (%)	QNEXA Top (N=295) n (%)	Total (N=675) n (%)
Nervous system disorders	17 (7.5)	16 (10.5)	42 (14.2)	75 (11.1)
Headache	6 (2.6)	4 (2.6)	12 (4.1)	22 (3.3)
Paraesthesia	0 (0.0)	1 (0.7)	10 (3.4)	11 (1.6)
Psychiatric disorders	16 (7.0)	19 (12.4)	28 (9.5)	63 (9.3)
Insomnia	8 (3.5)	9 (5.9)	11 (3.7)	28 (4.1)
Depression	2 (0.9)	3 (2.0)	10 (3.4)	15 (2.2)
Anxiety	3 (1.3)	3 (2.0)	6 (2.0)	12 (1.8)
Metabolism and nutrition disorders	28 (12.3)	13 (8.5)	21 (7.1)	62 (9.2)
Diabetes mellitus	7 (3.1)	1 (0.7)	3 (1.0)	11 (1.6)
Dyslipidemia	6 (2.6)	2 (1.3)	0 (0.0)	8 (1.2)
Investigations	18 (7.9)	11 (7.2)	23 (7.8)	52 (7.7)
Weight increased	5 (2.2)	0 (0.0)	7 (2.4)	12 (1.8)
Hemoglobin decreased	2 (0.9)	3 (2.0)	0 (0.0)	5 (0.7)
Abdominal bruit	0 (0.0)	3 (2.0)	1 (0.3)	4 (0.6)
General disorders and administration site conditions	13 (5.7)	10 (6.5)	25 (8.5)	48 (7.1)
Edema peripheral	7 (3.1)	0 (0.0)	12 (4.1)	19 (2.8)
Eye disorders	13 (5.7)	12 (7.8)	19 (6.4)	44 (6.5)
Eye pain	2 (0.9)	4 (2.6)	4 (1.4)	10 (1.5)
Vascular disorders	14 (6.2)	3 (2.0)	11 (3.7)	28 (4.1)
Hypertension	9 (4.0)	2 (1.3)	10 (3.4)	21 (3.1)
Immune system disorders	4 (1.8)	4 (2.6)	9 (3.1)	17 (2.5)
Seasonal allergy	2 (0.9)	3 (2.0)	6 (2.0)	11 (1.6)

Treatment-emergent adverse events = adverse events that started on or after the first dose of study drug in study OB-305 and up to 28 days after the last dose of study drug in Study OB-305.
QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

The second year of exposure to QNEXA did not result in any new or unexpected adverse events and the severity of observed events was comparable between the first and second years of exposure.

4.3.3.3 Targeted Medical Events

Table 33 summarizes targeted medical events by class and subclass for the 2-Year Cohort.

Table 33. Targeted Medical Events by Class and Subclass (Safety Set, 2-Year Cohort)

TME Class TME Subclass	Placebo (N=227) n (%)	QNEXA Mid (N=153) n (%)	QNEXA Top (N=295) n (%)
Psychiatric disorders class			
Sleep disorders subclass	25 (11.0)	22 (14.4)	38 (12.9)
Depression (SMQ) subclass[a]	18 (7.9)	6 (3.9)	24 (8.1)
Anxiety subclass	7 (3.1)	10 (6.5)	28 (9.5)
Cognitive disorders class			
Attention subclass	1 (0.4)	5 (3.3)	9 (3.1)
Memory impairment subclass	2 (0.9)	3 (2.0)	6 (2.0)
Language subclass	0 (0.0)	2 (1.3)	1 (0.3)
Other cognitive disorders NOS subclass	2 (0.9)	1 (0.7)	4 (1.4)
Cardiovascular disorders class			
Cardiac arrhythmia (SMQ) subclass	11 (4.8)	10 (6.5)	12 (4.1)
Ischemic heart disease (SMQ) subclass	1 (0.4)	2 (1.3)	3 (1.0)
Ophthalmic disorders class			
Ophthalmic disorders subclass	4 (1.8)	6 (3.9)	12 (4.1)
Menstrual disorders class			
Menstrual disorders subclass	5 (2.2)	5 (3.3)	8 (2.7)
Psychomotor disorders class			
Psychomotor disorders subclass	0 (0.0)	1 (0.7)	4 (1.4)

a. The SMQ for depression was modified to exclude adverse events associated with known mechanisms of action for phentermine or topiramate that may have confounded analysis of the given category.
NOS = not otherwise specified; QNEXA = fixed-dose combination of phentermine and topiramate;
SMQ = standardized Medical Dictionary for Regulatory Activities (MedDRA) query; TME = targeted medical event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In the psychiatric disorders class, a dose-related increase in the incidence of TEAEs categorized as anxiety was observed in the 2-Year Cohort. The incidence of TEAEs in the depression subclass was higher in the QNEXA Top dose group than in the other treatment groups. The incidence of TEAEs in the sleep disorders subclass was similar for the treatment groups. No subjects in any treatment group had a suicide/self-injury TEAE. Events in this class are further discussed in **Appendix 6**.

In the Cognitive Disorders class, the incidence of TEAEs in the attention and memory impairment subclasses was higher in the QNEXA Mid and Top dose groups than in the placebo groups. The incidence of TEAEs in the language and other cognitive disorders subclasses was low overall, but higher in the QNEXA Top dose group compared with the other treatment groups. Events in this class are further discussed in **Appendix 6**.

Unlike in the 1-Year Cohort, the incidence of TEAEs in the cardiac arrhythmia subclass in the 2-Year Cohort was similar in the QNEXA treatment groups and the placebo group. Most of the cardiac arrhythmia TEAEs were palpitations and syncope. For the 2-Year Cohort, the cardiac arrhythmia TEAE was serious for 2 subjects in the QNEXA Mid dose group; no subjects in the QNEXA Top dose group or the placebo group had a serious cardiac arrhythmia TEAE. The incidence of TEAEs in the ischemic heart disease subclass was low and similar

for the treatment groups. No adverse events of valvulopathy were observed. Events in the cardiac arrhythmia and ischemic heart disease subclasses are further discussed in Sections **5.2.3.1** and **5.2.3.2**.

4.3.3.4 Other Serious Adverse Events and Discontinuations Due to TEAEs

In total, 47 (7.0%) subjects in the 2-Year Cohort had a treatment-emergent SAE: 14 (6.2%) subjects in the placebo group, 9 (5.9%) subjects in the QNEXA Mid dose group, and 24 (8.1%) subjects in the QNEXA Top dose group. No subjects had a treatment-emergent SAE that was considered by the investigators to be related to study drug. A total of 27 (4.0%) subjects in the 2-Year Cohort discontinued study drug due to a TEAE in studies OB 303 and OB 305. The percentage of subjects who discontinued study drug due to a TEAE was similar for the treatment groups. In total, 11 (1.6%) subjects discontinued study drug due to a drug related TEAE.

4.3.3.5 Assessment of Depression (PHQ-9)

For the 2-year cohort, baseline depression severity as assessed by the PHQ-9 total score was similar for the treatment groups. At baseline, the PHQ-9 score indicated no clinical depression (score of 0–4) for the majority of subjects in each treatment group (from 74.4% to 81.0%). The baseline incidence of mild depression (score of 5–9) ranged from 14.4% to 20.3%. Few subjects in the 2-year cohort had a positive response to PHQ-9 Question 9 (“thoughts that you would be better off dead, or of hurting yourself in some way”) on several days after randomization. No subjects had a positive response to PHQ-9 Question 9 on more than half of the days or nearly every day after randomization. The percentages of subjects with a positive response to PHQ-9 Question 9 after randomization were similar for the treatment groups: 3 (1.3%) subjects in the placebo group, 2 (1.3%) subjects in the QNEXA Mid dose group, and 2 (0.7%) subjects in the QNEXA Top dose group.

4.3.3.6 Assessment of Suicidal Behavior and Suicidal Ideation (C-SSRS)

In the 2-year cohort, 6 (0.9%) subjects had a “yes” response to the C-SSRS categories of suicidal ideation and suicidality (suicidal behavior or suicidal ideation) during studies OB-303 and OB-305: 3 (1.3%) subjects in the placebo group, 1 (0.7%) subject in the QNEXA Mid dose group, and 2 (0.7%) subjects in the QNEXA Top dose group.

Four (0.6%) subjects had a “yes” response to the C-SSRS category of emergence of suicidal ideation during studies OB-303 and OB-305: 2 (0.9%) subjects in the placebo group, 1 (0.7%) subject in the QNEXA Mid dose group, and 1 (0.3%) subject in the QNEXA Top dose group.

Five (0.7%) subjects had a “yes” response to the C-SSRS category of worsening suicidal ideation during studies OB-303 and OB-305: 2 (0.9%) subjects in the placebo group, 1 (0.7%) subject in the QNEXA Mid dose group, and 2 (0.7%) subjects in the QNEXA Top dose group.

No subjects in the placebo group or QNEXA Mid dose group had a “yes” response to any C-SSRS category during study OB-305. Two (0.7%) subjects in the QNEXA Top dose group had a “yes” response to the C-SSRS categories of suicidal ideation, suicidality (suicidal

behavior or suicidal ideation), and worsening suicidal ideation during study OB-305. One (0.3%) subject in the QNEXA Top dose group had a "yes" response to the C-SSRS category of emergence of suicidal ideation during study OB-305.

No subjects had a "yes" response to any C-SSRS category at Week 108/Early Termination.

4.3.3.7 Clinical Laboratory Evaluations

The clinical laboratory evaluations for the 2-Year Cohort showed no adverse effects of QNEXA treatment on safety laboratory parameters. The numbers and percentages of subjects with significant elevations in liver function tests in the 2-Year Cohort were low, and no differences among the treatment groups were observed. No subjects in the 2-Year Cohort had changes in liver function tests and bilirubin that met Hy's Law criteria.

In the 2-Year Cohort, one (0.3%) subject in the QNEXA Top dose group had a serum bicarbonate level <17 mEq/L at two consecutive visits during studies OB-303 and OB-305 or at the last study visit.

5 REVIEW OF CARDIOVASCULAR SAFETY

5.1 Summary of Heart Rate, Blood Pressure, and Cardiovascular Adverse Events

This section summarizes all available data on heart rate changes in the QNEXA program. This includes a review of population, subgroup and outlier changes in heart rate. Data summarizing heart rate changes in the context of changes in blood pressure through assessment of rate-pressure product (RPP) are presented. In the context of the overall picture, predictive models of cardiovascular risk were explored using the Cooper Clinical Index and Framingham risk scores. These may provide a bridge between observed improvements in cardiovascular risk parameters weighed against heart rate changes in an individual. Finally, in order to assess the program-based risk associated with observed heart rate changes, an analysis of all major cardiovascular events are presented in the context of any association with heart rate effects.

5.1.1 Heart Rate and Blood Pressure Over Time

5.1.1.1 1-Year Cohort

Table 34 summarizes mean changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate from baseline to endpoint for the 1-Year Cohort. Mean decreases in SBP and DBP were observed for all of the treatment groups. The mean decreases in SBP were larger for the QNEXA groups than for the placebo group. The mean decreases in DBP were larger for the QNEXA Top dose group and QNEXA Mid dose group than for the placebo group.

A small, dose-related mean increase in heart rate was observed for QNEXA treatment groups over placebo (QNEXA Low dose, 1.3 bpm; QNEXA Mid dose, 0.6 bpm; QNEXA Top dose,

1.6 bpm). The difference in mean change in heart rate between QNEXA Top dose and placebo was statistically significant (p<0.0001).

Table 34. Changes in Blood Pressure and Heart Rate from Baseline to Endpoint – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Parameter Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Systolic blood pressure (mmHg)				
n[a]	1,532	234	488	1,553
Baseline[b] mean (SD)	126.5 (13.25)	122.5 (11.11)	128.5 (13.63)	125.7 (13.12)
Endpoint[c] mean (SD)	124.3 (13.64)	119.1 (12.24)	123.4 (14.08)	120.5 (13.50)
Mean change (SD)	-2.1 (14.01)	-3.3 (11.95)	-5.2 (14.77)	-5.2 (14.48)
Within-treatment p-value[d]	<0.0001	0.0003	<0.0001	<0.0001
Comparison to placebo p-value[d]	--	0.2322	<0.0001	<0.0001
Diastolic blood pressure (mmHg)				
n[a]	1,532	234	488	1,553
Baseline[b] mean (SD)	79.6 (8.95)	77.8 (7.49)	80.6 (8.71)	79.0 (8.76)
Endpoint[c] mean (SD)	77.7 (9.62)	76.9 (8.24)	77.3 (8.82)	76.1 (8.82)
Mean change (SD)	-1.9 (9.61)	-0.9 (8.29)	-3.3 (9.87)	-2.9 (9.40)
Within-treatment p-value[d]	<0.0001	0.1402	<0.0001	<0.0001
Comparison to placebo p-value[d]	--	0.1362	0.0044	0.0023
Heart rate (bpm)				
n[a]	1,532	234	488	1,553
Baseline[b] mean (SD)	72.5 (9.58)	72.3 (9.22)	72.2 (10.07)	72.7 (9.87)
Endpoint[c] mean (SD)	72.5 (10.05)	73.6 (9.73)	72.7 (10.34)	74.3 (9.83)
Mean change (SD)	0.0 (10.19)	1.3 (10.32)	0.6 (10.18)	1.6 (10.28)
Within-treatment p-value[d]	0.9861	0.0499	0.2238	<0.0001
Comparison to placebo p-value[d]	--	0.0688	0.2933	<0.0001

a. n is the number of subjects with baseline and endpoint measurements.
b. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
c. Endpoint is the last available measurement obtained during the double-blind treatment period.
d. p-values obtained from ANOVA model with treatment as a fixed effect.
QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

The percentages of subjects with categorical increases in SBP from baseline were lower in the QNEXA groups than in the placebo group. The percentages of subjects with categorical increases in heart rate from baseline were higher in the QNEXA groups than in the placebo group.

Table 35 summarizes the numbers and percentages of subjects in the 1-Year Cohort with consecutive categorical increases in SBP, DBP, and heart rate during the double-blind treatment period, defined as two or more consecutive visits above the given threshold. No meaningful differences were observed among treatment groups in the percentage of subjects with consecutive increases in SBP or DBP. The percentages of subjects with consecutive categorical increases in heart rate from baseline were higher in the QNEXA groups than in the placebo group.

Table 35. Consecutive Categorical Increases from Baseline in Blood Pressure and Heart Rate During Double-Blind Treatment – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Parameter Category	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Systolic blood pressure				
>5 mmHg	565 (36.2)	63 (26.3)	141 (28.3)	497 (31.5)
>10 mmHg	319 (20.4)	35 (14.6)	76 (15.3)	264 (16.7)
>15 mmHg	175 (11.2)	16 (6.7)	48 (9.6)	132 (8.4)
>20 mmHg	78 (5.0)	7 (2.9)	17 (3.4)	54 (3.4)
>25 mmHg	37 (2.4)	6 (2.5)	10 (2.0)	19 (1.2)
>30 mmHg	14 (0.9)	2 (0.8)	3 (0.6)	11 (0.7)
Diastolic blood pressure				
>5 mmHg	430 (27.5)	74 (30.8)	130 (26.1)	452 (28.6)
>10 mmHg	172 (11.0)	22 (9.2)	55 (11.0)	182 (11.5)
>15 mmHg	63 (4.0)	6 (2.5)	17 (3.4)	61 (3.9)
>20 mmHg	14 (0.9)	0 (0.0)	3 (0.6)	10 (0.6)
Heart rate				
>5 bpm	562 (36.0)	103 (42.9)	230 (46.2)	797 (50.4)
>10 bpm	254 (16.3)	59 (24.6)	113 (22.7)	434 (27.5)
>15 bpm	117 (7.5)	29 (12.1)	39 (7.8)	213 (13.5)
>20 bpm	42 (2.7)	9 (3.8)	13 (2.6)	72 (4.6)

Consecutive increases are defined as increases in blood pressure or heart rate from baseline at two or more consecutive visits for the given threshold.
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Among subjects with hypertension in study OB-303, 3.9% and 4.3% of QNEXA Mid dose and QNEXA Top dose subjects, compared with 8.1% of placebo subjects, started new anti-hypertensive medications. Conversely, 10.5% and 14.8% of QNEXA Mid dose and QNEXA Top dose subjects, compared with 4.7% of placebo subjects, discontinued existing anti-hypertensive medications.

5.1.1.2 2-Year Cohort

Table 36 summarizes mean changes in SBP, DBP, and heart rate from baseline to Week 108 for the 2-Year Cohort. All of the treatment groups had mean decreases in SBP and DBP from baseline. The mean decreases in SBP and DBP were similar for the treatment groups. Small mean increases in heart rate were observed in all treatment groups. None of the comparisons of mean change in heart rate between the placebo and QNEXA treatment groups were statistically significant. Consistent with study OB-303, the percentage of subjects who had an increase in the number of concomitant antihypertensive medications during the 2-year treatment period was higher in the placebo group than in the QNEXA groups and the percentage of subjects with a decrease in the number of concomitant antihypertensive medications was higher in the QNEXA groups than in the placebo group.

Table 36. Changes in Blood Pressure and Heart Rate from Baseline to Week 108 (Safety Set, 2-Year Cohort)

Parameter Statistic	Placebo (N=227)	QNEXA Mid (N=153)	QNEXA Top (N=295)
Systolic blood pressure (mmHg)			
n[a]	197	129	248
Baseline[b] mean (SD)	128.4 (14.45)	127.9 (11.71)	126.4 (13.61)
Week 108 mean (SD)	124.1 (12.44)	122.9 (13.44)	122.6 (12.81)
Mean change (SD)	-4.2 (15.12)	-5.0 (14.29)	-3.9 (14.00)
Within-treatment p-value[c]	<0.0001	<0.0001	<0.0001
Comparison to placebo p-value[c]	--	0. 6276	0.7760
Diastolic blood pressure (mmHg)			
n[a]	197	129	248
Baseline[b] mean (SD)	79.7 (9.55)	79.8 (9.09)	79.5 (8.69)
Week 108 mean (SD)	76.1 (9.34)	76.3 (8.76)	76.6 (8.24)
Mean change (SD)	-3.6 (10.27)	-3.5 (9.62)	-2.9 (9.44)
Within-treatment p-value[c]	<0.0001	<0.0001	<0.0001
Comparison to placebo p-value[c]	--	0.9477	0.4861
Heart rate (bpm)			
n[a]	197	129	248
Baseline[b] mean (SD)	70.6 (10.25)	72.2 (9.67)	73.0 (10.27)
Week 108 mean (SD)	71.0 (9.63)	73.4 (9.68)	74.8 (9.49)
Mean change (SD)	0.4 (9.86)	1.3 (10.17)	1.7 (10.64)
Within-treatment p-value[c]	0.5650	0.1654	0.0076
Comparison to placebo p-value[c]	--	0.4734	0.1771

a. n is the number of subjects with measurements at both baseline and Week 108.
b. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303.
c. p-values obtained from ANOVA model with treatment as a fixed effect.
QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

In the 2-Year Cohort the percentages of subjects with categorical increases in SBP from baseline were lower in the QNEXA groups than in the placebo group. The percentages of subjects with increases in DBP >15 mmHg and >20 mmHg were lower in the QNEXA groups than in the placebo group. The percentages of subjects with increases in heart rate >5 bpm, >10 bpm, and >15 bpm were lower in the placebo group than in the QNEXA groups.

Table 37 presents the numbers and percentages of subjects in the 2-Year Cohort with consecutive categorical increases in SBP, DBP, and heart rate from baseline during studies OB-303 and OB-305. The percentages of subjects with consecutive increases in SBP >15 mmHg, >20 mmHg, >25 mmHg, and >30 mmHg were lower in the QNEXA groups than in the placebo group. The percentages of subjects with consecutive increases in DBP >20 mmHg were lower in the QNEXA groups than in the placebo group. The percentages of subjects with consecutive increases in heart rate >5 bpm, >10 bpm, and >15 bpm were lower in the placebo group than in the QNEXA groups. No differences between the placebo and QNEXA treatment groups were observed for heart rate elevations >20 bpm over the baseline value.

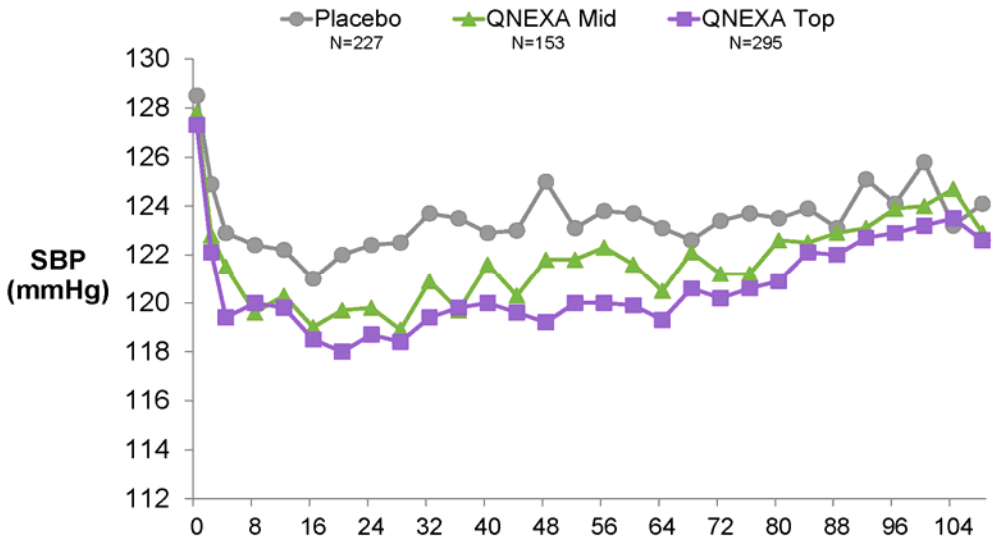
Table 37. Consecutive Categorical Increases from Baseline in Blood Pressure and Heart Rate from Baseline (Safety Set, 2-Year Cohort)

Parameter Category	Placebo (N=227) n (%)	QNEXA Mid (N=153) n (%)	QNEXA Top (N=295) n (%)
Systolic blood pressure			
>5 mmHg	114 (50.2)	66 (43.1)	130 (44.1)
>10 mmHg	65 (28.6)	43 (28.1)	78 (26.4)
>15 mmHg	39 (17.2)	23 (15.0)	38 (12.9)
>20 mmHg	21 (9.3)	8 (5.2)	13 (4.4)
>25 mmHg	9 (4.0)	2 (1.3)	5 (1.7)
>30 mmHg	3 (1.3)	0 (0.0)	3 (1.0)
Diastolic blood pressure			
>5 mmHg	82 (36.1)	56 (36.6)	112 (38.0)
>10 mmHg	37 (16.3)	23 (15.0)	48 (16.3)
>15 mmHg	18 (7.9)	11 (7.2)	16 (5.4)
>20 mmHg	8 (3.5)	2 (1.3)	3 (1.0)
Heart rate			
>5 bpm	122 (53.7)	93 (60.8)	192 (65.1)
>10 bpm	60 (26.4)	46 (30.1)	108 (36.6)
>15 bpm	28 (12.3)	22 (14.4)	59 (20.0)
>20 bpm	12 (5.3)	8 (5.2)	19 (6.4)

Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in Study OB-303.
All measurements taken during the randomized, double-blind treatment period of Studies OB-303 and OB-305 were considered.
Consecutive increases were increases in blood pressure or heart rate from baseline that were above the given threshold at two or more consecutive visits.
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

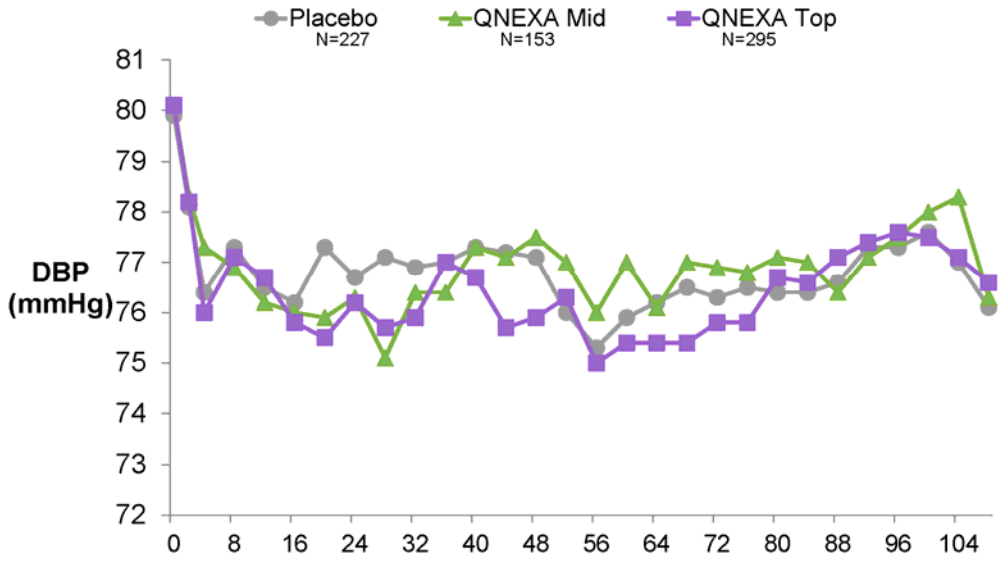
Considering SBP, DBP and heart rate over time for the 2-Year Cohort, mean SBP was lower in the QNEXA groups than in the placebo group. Mean DBP was similar across treatment groups over the first 60 weeks and then slightly lower in the QNEXA groups than in the placebo group over the final 48 weeks. Mean heart rate was slightly higher in the QNEXA groups than in the placebo group at baseline and during study. For the QNEXA groups, mean heart rate elevations were highest over the first 12 weeks of the study and then returned to at or near baseline levels over the remaining 96 weeks. For the placebo group, mean heart rate was elevated over the first 4 weeks and then decreased over the remainder of the double-blind treatment period (**Figure 23**, **Figure 24**, and **Figure 25**).

Figure 23. Changes in Systolic Blood Pressure Over Time (Safety Set, 2-Year Cohort)



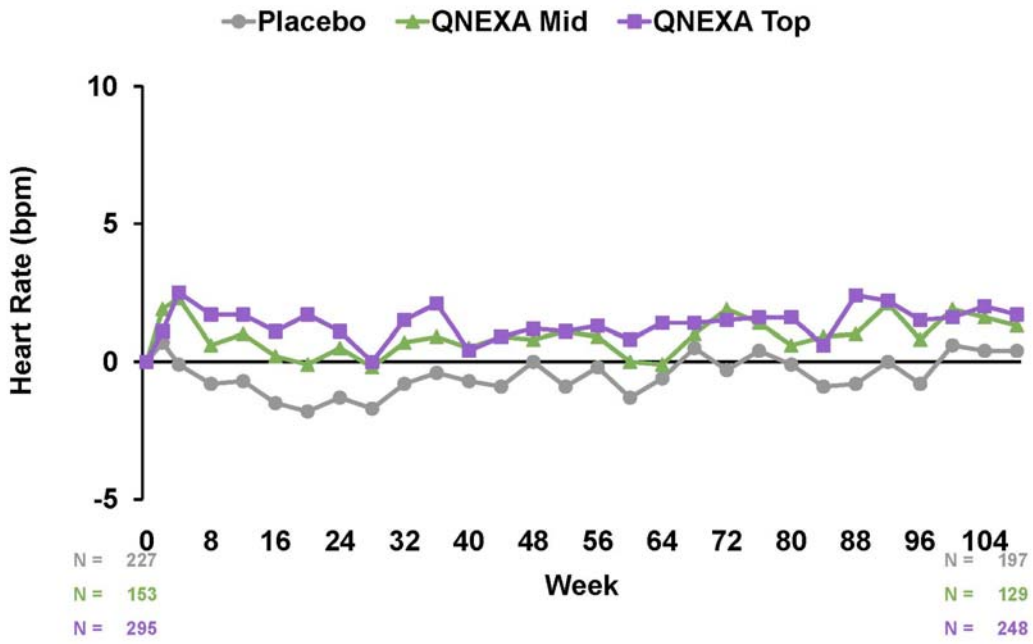
QNEXA = fixed-dose combination of phentermine and topiramate; SBP = systolic blood pressure
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Figure 24. Changes in Diastolic Blood Pressure Over Time (Safety Set, 2-Year Cohort)



QNEXA = fixed-dose combination of phentermine and topiramate; DBP = diastolic blood pressure
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Figure 25. Changes in Heart Rate Over Time (Safety Set, 2-Year Cohort)



QNEXA = fixed-dose combination of phentermine and topiramate
QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

5.1.2 Heart Rate and Blood Pressure by Baseline Risk Category

5.1.2.1 Changes in Blood Pressure and Heart Rate by Baseline Risk Category

For purposes of examining differences in heart rate, blood pressure or adverse events in various baseline risk populations, subjects in the 1-Year Cohort were classified into modified ATP III cardiovascular risk categories at baseline of high, medium, or low based on the following criteria:

- High Risk: subjects with CVD defined as a history of coronary artery disease, peripheral arterial occlusive disease, or stroke; or subjects with diabetes mellitus and 1 or both of the following risk factors for CVD: hypertension or dyslipidemia;
- Medium Risk: subjects with CVD risk factors only: hypertension, dyslipidemia, or diabetes mellitus;
- Low Risk: subjects with none of the above.

Table 38 summarizes mean changes in SBP, DBP, and heart rate from baseline to Week 56/Early Termination for subgroups of subjects by baseline cardiovascular risk category in the 1-Year Cohort. Mean reductions in SBP and DBP were observed in most treatment groups. Across all baseline risk subgroups, treatment with QNEXA Mid dose and QNEXA Top dose resulted in larger mean reductions in SBP and DBP than treatment with placebo. For all QNEXA treatment groups, the smallest mean increases in heart rate were observed in subjects in the high baseline risk category. Within the high baseline risk

subgroup, no meaningful differences in mean heart rate increases were observed between the placebo and QNEXA treatment groups.

Table 38. Changes in Blood Pressure and Heart Rate from Baseline to Week 56/Early Termination – Baseline Cardiovascular Risk Subgroups (Safety Set, 1-Year Cohort)

Parameter Subgroup	Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Change in systolic blood pressure (mmHg)					
Low baseline risk	n Mean (SD)	281 -0.2 (11.63)	114 -2.5 (11.74)	30 -4.9 (12.72)	327 -3.9 (11.99)
Medium baseline risk	n Mean (SD)	1,025 -2.5 (14.58)	115 -3.6 (11.73)	385 -5.4 (14.45)	973 -5.7 (14.48)
High baseline risk	n Mean (SD)	226 -2.8 (13.96)	5 -15.4 (17.04)	73 -3.8 (17.15)	253 -5.2 (17.10)
Change in diastolic blood pressure (mmHg)					
Low baseline risk	n Mean (SD)	281 -0.1 (8.10)	114 0.1 (8.76)	30 -2.6 (7.51)	327 -2.0 (8.64)
Medium baseline risk	n Mean (SD)	1,025 -2.3 (9.93)	115 -1.7 (7.76)	385 -3.4 (9.89)	973 -3.3 (9.53)
High baseline risk	n Mean (SD)	226 -2.4 (9.68)	5 -6.6 (5.27)	73 -3.3 (10.65)	253 -2.9 (9.78)
Change in heart rate (bpm)					
Low baseline risk	n Mean (SD)	281 -0.3 (10.27)	114 1.9 (10.63)	30 1.7 (8.58)	327 1.7 (9.81)
Medium baseline risk	n Mean (SD)	1,025 -0.1 (10.16)	115 0.8 (10.23)	385 0.5 (10.27)	973 1.7 (10.57)
High baseline risk	n Mean (SD)	226 0.7 (10.21)	5 0.6 (3.13)	73 0.5 (10.40)	253 1.2 (9.73)

n is the number of subjects with measurements at both baseline and Week 108.
Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in Study OB-303.
QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

5.1.2.2 Changes in Heart Rate by Baseline Heart Rate

In addition to categorizing subjects into baseline risk categories, subgroups were also created using baseline heart rate. Subgroups were defined by baseline heart rate <60 bpm, baseline heart rate between 60 bpm and 90 bpm, inclusive, and baseline heart rate >90 bpm.

Table 39 summarizes changes in heart rate from baseline to Week 56/Early Termination for the subgroups of subjects by baseline heart rate category. For subjects with baseline heart rate <60 bpm, mean increases in heart rate were observed in all treatment groups. For subjects with baseline heart rate between 60 bpm and 90 bpm, small mean increases in heart rate were observed in all treatment groups. For subjects with baseline heart rate >90 bpm, mean decreases in heart rate were observed in all treatment groups.

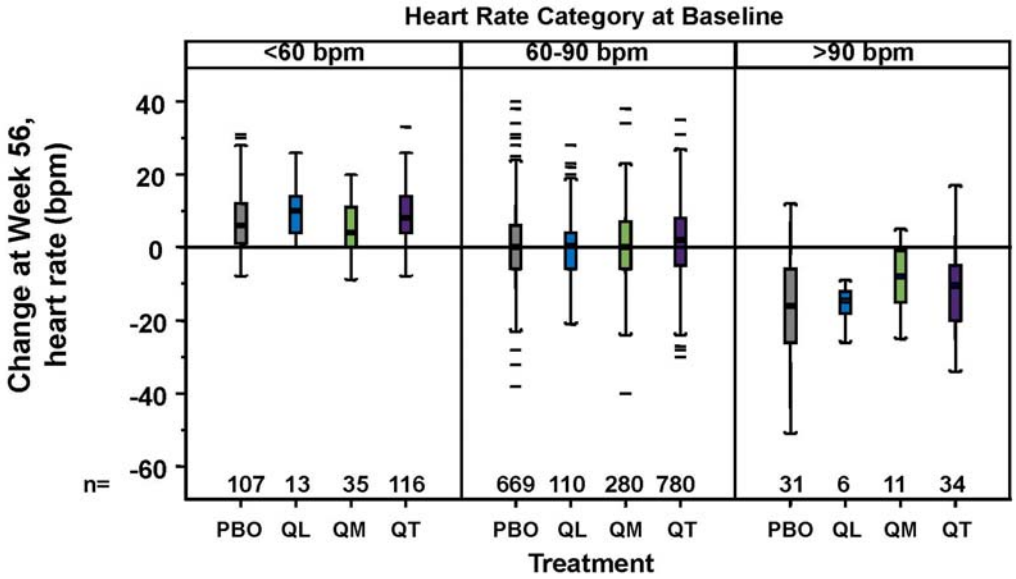
Table 39. Changes in Heart Rate from Baseline to Week 56/Early Termination – Baseline Heart Rate Subgroups (Safety Set, 1-Year Cohort)

Parameter Subgroup	Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Change in heart rate (bpm)					
Baseline heart rate <60 bpm	n Mean (SD)	96 7.5 (10.39)	12 12.6 (13.52)	27 6.2 (6.15)	107 9.3 (8.89)
Baseline heart rate ≥60 bpm to ≤90 bpm	n Mean (SD)	1378 0.1 (9.49)	215 1.2 (9.50)	438 0.9 (9.68)	1384 1.7 (9.70)
Baseline heart rate >90 bpm	n Mean (SD)	58 -13.7 (12.13)	7 -14.4 (6.29)	23 -12.6 (12.85)	62 -11.9 (11.40)

n is the number of subjects with measurements at both baseline and Week 108.
Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303.
QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Figure 26 presents side-by-side boxplots for change in heart rate from baseline to Week 56/Early Termination by baseline heart rate category. The mean increases in heart rate observed in the 1-Year Cohort do not appear to occur in the subgroup of subjects in whom they would cause the most safety concern – those with the highest baseline heart rates. For subjects with the highest baseline heart rate (>90 bpm), most subjects had a lower heart rate at Week 56/Early Termination.

Figure 26. Change in Heart Rate by Baseline Heart Rate Category (Safety Set, 1-Year Cohort



PBO = placebo; QL = QNEXA Low dose; QM = QNEXA Mid dose;
QNEXA = fixed-dose combination of phentermine and topiramate; QT = QNEXA Top dose
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

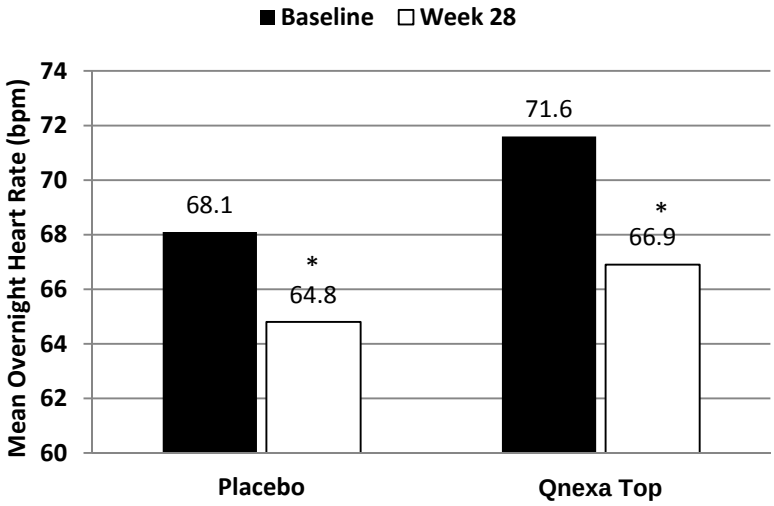
5.1.3 Subgroup Analyses of Heart Rate and Blood Pressure

Changes in SBP, DBP, and heart rate from baseline to Week 56/Early Termination were analyzed for multiple subgroups to attempt to identify any segment of the population that might be at greater risk for elevations in heart rate or blood pressure. The subgroups analyzed included: age (<60 years, ≥60 years); gender (male, female); race (Black, non-Black); body mass index (BMI) (<40 kg/m^2, ≥40 kg/m^2); diabetes at baseline (with, without); persistent serum bicarbonate reductions (defined as serum bicarbonate <21 mEq/L at two or more consecutive visits) during double-blind treatment (with, without); concomitant medication usage (with, without) including beta blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, calcium channel blockers, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors; and weight loss category at Week 56 (≤0%, >0% to <5%, ≥5% to <10%, ≥10%).

5.1.4 Overnight Heart Rate Changes in Sleep Apnea Patients

Based on these analyses, no subgroup appeared to be at a higher risk for heart rate or blood pressure elevations **(Figure 27)**. In general, greater reductions in SBP and DBP were observed for Mid and Top dose treated subjects compared to placebo.

Figure 27. Mean Overnight Heart Rate (bpm) During Continuous Overnight Polysomnography – OB-204



* = significant change from baseline within treatment group.
Note: comparison of placebo to QNEXA Top dose was not significant.

These data demonstrate that treatment with QNEXA Top dose reduced night time heart rate by 1.5 bpm compared to placebo. In addition, in subjects treated with QNEXA Top dose, the deceleration in heart rate observed at night is at least as large; if not larger than for placebo-treated subjects. The absence of night-time decelerations in heart rate is a predictor of major cardiovascular events; thus, the nocturnal pattern of heart rate changes in this study is not suggestive of an adverse effect (Verdecchia 1998; Ben-Dov 2007).

5.2 Summary of Heart Rate, Blood Pressure, and Cardiovascular Adverse Events – Subjects with and without Heart Rate Elevations during Double-Blind Treatment

Subgroup analyses were performed for the subgroups of subjects with and without heart rate elevations (>10 bpm over baseline at two or more consecutive visits or heart rate >90 bpm at two consecutive visits) during the double-blind treatment period. Changes in heart rate, as well as adverse events and changes in weight, blood pressure, lipids, and C-reactive protein (CRP) were summarized for both subgroups.

5.2.1 Subgroup Changes in Heart Rate

Table 40 summarizes mean changes in heart rate from baseline to Week 56/Early Termination for the subgroups of subjects with and without heart rate elevations during the double-blind treatment period in the 1-Year Cohort.

For the subgroup of subjects with heart rate elevations, significant and dose-related reductions in SBP were observed. The mean reduction in SBP for subjects treated with QNEXA Top dose was larger for subjects with heart rate elevations than for subjects without heart rate elevations.

Diastolic blood pressure decreased in nearly all treatment groups for both heart rate elevation subgroups, with larger reductions observed in the QNEXA Mid dose group and the QNEXA Top dose group compared to the placebo group for both subgroups.

For subjects with heart rate elevations, the mean and median increases in heart rate were similar for the placebo group and QNEXA Top dose group. For subjects without heart rate elevations, similar mean reductions were observed in the placebo and QNEXA Top dose groups.

Table 40. Changes in Blood Pressure and Heart Rate from Baseline to Week 56/Early Termination – Heart Rate Elevation Subgroups – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Parameter Subgroup Statistic	Placebo	QNEXA Low	QNEXA Mid	QNEXA Top
Systolic Blood Pressure (mmHg)				
With Heart Rate Elevations				
n[a]	284	65	132	488
Baseline[b] mean (SD)	126.7 (13.13)	122.0 (11.71)	129.1 (14.47)	125.3 (13.14)
Endpoint[c] mean (SD)	124.3 (12.92)	119.5 (12.85)	124.8 (14.17)	118.7 (13.14)
Mean change (SD)	-2.5 (14.88)	-2.5 (12.96)	-4.3 (16.32)	-6.6 (14.43)
Median (Min, Max) change	-2.0 (-39, 46)	-4.0 (-36, 46)	-4.0 (-42, 64)	-6.0 (-49, 35)
Without Heart Rate Elevations				
n[a]	1248	169	356	1065
Baseline[b] mean (SD)	126.4 (13.28)	122.7 (10.90)	128.3 (13.32)	125.9 (13.11)
Endpoint[c] mean (SD)	124.4 (13.80)	119.0 (12.04)	122.9 (14.04)	121.3 (13.58)
Mean change (SD)	-2.1 (13.81)	-3.6 (11.56)	-5.5 (14.16)	-4.6 (14.46)
Median (Min, Max) change	-2.0 (-59, 46)	-4.0 (-44, 41)	-5.5 (-45, 36)	-4.0 (-76, 53)
Diastolic Blood Pressure (mmHg)				
With Heart Rate Elevations				
n[a]	284	65	132	488
Baseline[b] mean (SD)	80.0 (9.11)	76.3 (8.00)	81.0 (9.47)	78.9 (8.73)
Endpoint[c] mean (SD)	78.0 (9.66)	77.1 (8.28)	77.8 (9.53)	75.6 (8.81)
Mean change (SD)	-2.0 (9.99)	0.9 (8.25)	-3.2 (11.05)	-3.3 (9.58)
Median (Min, Max) change	-2.0 (-37, 30)	1.0 (-16, 18)	-4.0 (-32, 38)	-4.0 (-31, 26)
Without Heart Rate Elevations				
n[a]	1248	169	356	1065
Baseline[b] mean (SD)	79.5 (8.91)	78.4 (7.22)	80.5 (8.42)	79.1 (8.77)
Endpoint[c] mean (SD)	77.7 (9.61)	76.8 (8.25)	77.2 (8.56)	76.3 (8.81)
Mean change (SD)	-1.9 (9.53)	-1.6 (8.22)	-3.4 (9.41)	-2.8 (9.32)
Median (Min, Max) change	-2.0 (-53, 34)	-1.0 (-20, 28)	-3.0 (-30, 29)	-3.0 (-31, 30)
Heart rate (bpm)				
With Heart Rate Elevations				
n[a]	284	65	132	488
Baseline[b] mean (SD)	69.2 (11.05)	68.6 (9.81)	69.7 (11.63)	70.0 (11.06)
Endpoint[c] mean (SD)	77.0 (12.41)	76.4 (10.90)	75.7 (11.43)	78.2 (10.75)
Mean change (SD)	7.9 (9.94)	7.9 (10.33)	6.1 (11.74)	8.3 (9.50)
Median (Min, Max) change	8.0 (-16, 59)	6.0 (-14, 46)	7.0 (-42, 38)	8.0 (-30, 35)
Without Heart Rate Elevations				
n[a]	1248	169	356	1065
Baseline[b] mean (SD)	73.2 (9.05)	73.7 (8.58)	73.1 (9.28)	73.9 (9.00)
Endpoint[c] mean (SD)	71.4 (9.13)	72.5 (9.04)	71.6 (9.68)	72.5 (8.83)
Mean change (SD)	-1.8 (9.37)	-1.2 (9.16)	-1.5 (8.72)	-1.4 (9.14)
Median (Min, Max) change	-2.0 (-51, 40)	0.0 (-26, 26)	-1.0 (-40, 22)	-1.0 (-34, 30)

a. n is the number of subjects with baseline and endpoint measurements.
b. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
c. Endpoint is the last available measurement obtained during the double-blind treatment period.
ET = early termination; QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

5.2.2 Overview of Adverse Events

Table 41 provides an overview of adverse events for the subgroups of subjects with and without heart rate elevations during the double-blind treatment period.

No important differences between the heart rate subgroups in the overall incidence of treatment-emergent adverse events (TEAEs), drug-related TEAEs, or distribution of TEAEs by maximum severity were observed.

For each treatment group, the incidences of adverse events that resulted in study drug discontinuation were higher for subjects without heart rate elevations compared to subjects with heart rate elevations.

For subjects with heart rate elevations, no specific treatment-emergent serious adverse event (SAE) occurred in more than 2 subjects in any treatment group.

Table 41. Overview of Adverse Events – Heart Rate Elevation Subgroups – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

	Subjects With Heart Rate Elevations				Subjects Without Heart Rate Elevations			
	Placebo (N=284) n (%)	QNEXA Low (N=65) n (%)	QNEXA Mid (N=132) n (%)	QNEXA Top (N=488) n (%)	Placebo (N=1,277) n (%)	QNEXA Low (N=175) n (%)	QNEXA Mid (N=366) n (%)	QNEXA Top (N=1,092) n (%)
Subjects with TEAEs								
Any TEAE	239 (84.2)	51 (78.5)	114 (86.4)	440 (90.2)	947 (74.2)	141 (80.6)	310 (84.7)	937 (85.8)
Any drug-related TEAE	70 (24.6)	26 (40.0)	61 (46.2)	277 (56.8)	363 (28.4)	74 (42.3)	190 (51.9)	643 (58.9)
Maximum severity of TEAEs								
Mild	106 (37.3)	14 (21.5)	45 (34.1)	180 (36.9)	385 (30.1)	46 (26.3)	106 (29.0)	344 (31.5)
Moderate	111 (39.1)	33 (50.8)	58 (43.9)	206 (42.2)	450 (35.2)	74 (42.3)	160 (43.7)	450 (41.2)
Severe	22 (7.7)	4 (6.2)	11 (8.3)	54 (11.1)	112 (8.8)	21 (12.0)	44 (12.0)	143 (13.1)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with SAEs								
Any SAE	9 (3.2)	1 (1.5)	8 (6.1)	19 (3.9)	46 (3.6)	5 (2.9)	7 (1.9)	48 (4.4)
Any treatment-emergent SAE	8 (2.8)	1 (1.5)	8 (6.1)	16 (3.3)	44 (3.4)	5 (2.9)	6 (1.6)	41 (3.8)
Any drug-related SAE	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.3)	1 (0.6)	1 (0.3)	7 (0.6)
Study drug discontinuations due to adverse events								
Any adverse event	23 (8.1)	6 (9.2)	13 (9.8)	58 (11.9)	109 (8.5)	22 (12.6)	45 (12.3)	218 (20.0)
Any TEAE	22 (7.7)	6 (9.2)	13 (9.8)	58 (11.9)	109 (8.5)	21 (12.0)	45 (12.3)	216 (19.8)
Any drug-related TEAE	11 (3.9)	5 (7.7)	5 (3.8)	37 (7.6)	71 (5.6)	14 (8.0)	37 (10.1)	173 (15.8)
Any SAE	2 (0.7)	1 (1.5)	3 (2.3)	4 (0.8)	13 (1.0)	1 (0.6)	1 (0.3)	14 (1.3)

Treatment-emergent adverse events were defined as adverse events that started on or after the first dose of double-blind study drug and up to 28 days after the last dose.
QNEXA = fixed-dose combination of phentermine and topiramate; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

5.2.3 Targeted Medical Events

5.2.3.1 Cardiac Arrhythmia Events

As shown in **Table 42**, the incidence of TEAEs in the cardiac arrhythmia subclass was higher in the QNEXA Mid and Top dose groups than in the QNEXA Low dose and placebo groups. There was no difference in the incidence of severe cardiac arrhythmia TEAEs among the treatment groups. Most of the TEAEs in this subclass were events associated with changes in heart rate, such as palpitations and were generally mild or moderate in severity for all treatment groups.

Cardiac arrhythmia TEAEs were serious in 4 (0.3%) subjects in the placebo group, 2 (0.4%) subjects in the QNEXA Mid dose group, and 2 (0.1%) subjects in the QNEXA Top dose group. Of the 98 subjects on QNEXA treatment who had a cardiac arrhythmia TEAE, 15 subjects discontinued study drug due to the TEAE. Of the 28 placebo-treated subjects who had a cardiac arrhythmia TEAE, 6 discontinued study drug due to the TEAE.

Table 42. Incidence of Treatment-Emergent Adverse Events in the Cardiac Arrhythmia Subclass – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Cardiac arrhythmia subclass	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)
Palpitations	12 (0.8)	2 (0.8)	12 (2.4)	27 (1.7)
Heart rate increased	1 (0.1)	0	2 (0.4)	12 (0.8)
Tachycardia	1 (0.1)	1 (0.4)	2 (0.4)	11 (0.7)
Syncope	4 (0.3)	0	2 (0.4)	6 (0.4)
Atrial fibrillation	2 (0.1)	0	1 (0.2)	3 (0.2)
Syncope vasovagal	0	0	2 (0.4)	3 (0.2)
Bundle branch block right	2 (0.1)	0	1 (0.2)	1 (0.1)
Arrhythmia	0	0	1 (0.2)	2 (0.1)
Electrocardiogram abnormal	3 (0.2)	0	0	0
Ventricular extrasystoles	1 (0.1)	0	0	2 (0.1)
Atrioventricular block first degree	1 (0.1)	0	0	1 (0.1)
Electrocardiogram QT prolonged	1 (0.1)	0	0	1 (0.1)
ECG repolarization abnormality	0	0	0	2 (0.1)
Heart rate irregular	0	0	0	2 (0.1)
Loss of consciousness	0	0	1 (0.2)	1 (0.1)
Bradycardia	0	0	0	1 (0.1)
Cardiac flutter	0	0	0	1 (0.1)
Cardiorespiratory arrest	1 (0.1)	0	0	0
Extrasystoles	0	0	0	1 (0.1)
Sinus bradycardia	0	1 (0.4)	0	0
Sinus tachycardia	0	0	0	1 (0.1)
Supraventricular extrasystoles	0	0	1 (0.2)	0

ECG = electrocardiogram; QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

5.2.3.2 Ischemic Events

The incidence of serious ischemic events is shown by treatment group in **Table 43**. In the total study population in the 1-Year Cohort (N=3,879), there were 16 SAEs in the Cardiac Disorders SOC, the majority of which were related to cardiac ischemia. The frequency of these ischemic events was similar in placebo and QNEXA treatment groups.

Table 43. Incidence of Serious Ischemic Events – Studies OB-202/DM-230, OB-302, and OB-303 (Safety Set, 1-Year Cohort)

Preferred Term	Placebo (N=1,561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1,580) n (%)
Cardiac disorders	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)
Coronary artery disease	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.1)
Angina pectoris	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood CPK increase	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Arteriosclerosis coronary artery	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cardio-respiratory arrest	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Overall, four SAEs were coded as myocardial infarction (MI) in active treatment arms (N=2,318), compared with none in the placebo group (N=1,561). Additionally, four SAEs of coronary artery disease were reported in placebo subjects, and none were reported in QNEXA-treated subjects: one angina event in the placebo group and one in the QNEXA group; one acute coronary syndrome in the QNEXA group; and one myocardial ischemia in the placebo group. The only study death – a sudden cardiac death – occurred in a placebo subject. Detailed narratives of cardiac SAEs are provided in **Appendix 5**.

For subjects with heart rate elevations, the incidence of TEAEs in the cardiac arrhythmia targeted medical event subclass was 0.7% for the placebo group, 3.1% for the QNEXA Low dose group, 7.6% for the QNEXA Mid dose group, and 5.5% for the QNEXA Top dose group. For subjects without heart rate elevations, the incidence of TEAEs in the cardiac arrhythmia targeted medical event subclass was 2.0% for the placebo group, 0.6% for the QNEXA Low dose group, 3.0% for the QNEXA Mid dose group, and 4.3% for the QNEXA Top dose group. Most of the TEAEs in the cardiac arrhythmia subclass were TEAEs of palpitations, increased heart rate, tachycardia, and syncope (preferred terms) and most were mild or moderate in severity for all of the treatment groups. For subjects with heart rate elevations, 1 severe TEAE of atrial fibrillation was reported in the QNEXA Mid dose group and 1 severe TEAE of syncope vasovagal was reported in the QNEXA Top dose group. No other severe TEAEs in the cardiac arrhythmia subclass were reported for subjects with heart rate elevations.

For subjects with heart rate elevations, the incidence of TEAEs in the ischemic heart disease targeted medical event subclass was 0.4% for the placebo group, 1.5% for the QNEXA Low dose group, 1.5% for the QNEXA Mid dose group, and 0.2% for the QNEXA Top dose group. For subjects without heart rate elevations, the incidence of TEAEs in the ischemic heart disease targeted medical event subclass was 0.5% for the placebo group, 0.0% for the QNEXA Low dose group, 0.3% for the QNEXA Mid dose group, and 0.3% for the QNEXA Top dose group.

5.3 Rate Pressure Product

A mechanism by which increased heart rate is believed to lead to an increased frequency of cardiac ischemia is through an increase in myocardial oxygen demand. The rate-pressure product is defined as the product of heart rate (bpm) and SBP (mmHg) divided by 1,000, and has been show to correlate with myocardial oxygen demand (White 1999). To evaluate heart rate effects of QNEXA in the context of blood pressure and ultimately, impact on myocardial oxygen demand, RPP changes were evaluated in the 1-year study cohort.

5.3.1 1-Year Cohort and Heart Rate Elevation Subgroups

Table 44 presents results for change in RPP from baseline to Week 56 with LOCF for the 1-Year Cohort, for the subgroups of subjects with and without heart rate elevations during the double-blind treatment period, and for subjects with and without hypertension at baseline.

For the 1-Year Cohort, statistically significant mean reductions in RPP were observed in the placebo, QNEXA Mid dose, and QNEXA Top dose groups. None of the comparisons between placebo and QNEXA treatment groups for change in RPP were statistically significant.

For subjects with heart rate elevations during the double-blind treatment period, statistically significant increases from baseline in RPP were observed in all treatment groups. The comparison of mean change in RPP between the placebo group and the QNEXA Top dose group was statistically significant (p=0.0118).

For subjects without heart rate elevations during the double-blind treatment period, statistically significant decreases from baseline in RPP were observed in all treatment groups. The comparison of mean change in RPP between the placebo group and the QNEXA Top dose group was statistically significant (p=0.0478).

For subjects with hypertension at baseline, statistically significant mean reductions in RPP were observed in the placebo, QNEXA Mid dose, and QNEXA Top dose groups. None of the comparisons between placebo and QNEXA treatment groups for change in RPP were statistically significant.

For subjects without hypertension at baseline, small mean changes in RPP were observed in all treatment groups. None of the comparisons between placebo and QNEXA treatment groups for change in RPP were statistically significant.

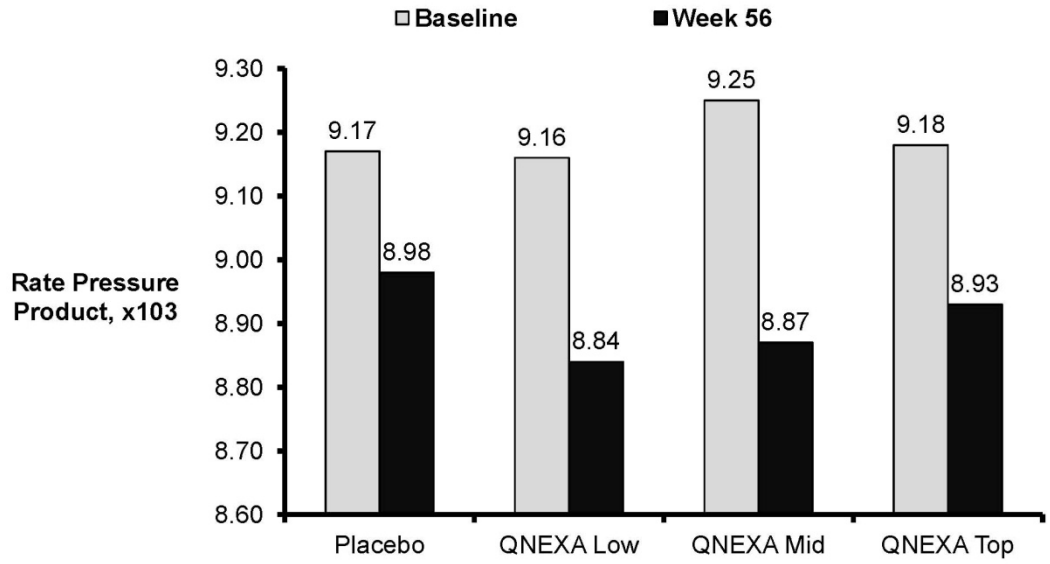
Table 44. Change in Rate-Pressure Product at Week 56 – Heart Rate Subgroups, and Hypertension Subgroups (Safety Set, 1-Year Cohort)

Treatment	N[a]	Baseline[b] Mean (SD)	Week 56 With LOCF[c] Mean (SD)	Change[d]			
				Mean (SD)	LS Mean (SE)	P-value Within	P-value vs Placebo
1-Year Cohort							
Placebo	1,531	9.16 (1.55)	9.01 (1.61)	-0.15 (1.67)	-0.13 (0.05)	0.0173	--
QNEXA Low	234	8.86 (1.46)	8.77 (1.47)	-0.09 (1.54)	-0.19 (0.11)	0.0751	0.5470
QNEXA Mid	488	9.27 (1.59)	8.97 (1.63)	-0.30 (1.73)	-0.23 (0.08)	0.0044	0.1686
QNEXA Top	1,551	9.14 (1.58)	8.95 (1.52)	-0.19 (1.69)	-0.18 (0.05)	0.0007	0.3306
Subjects With Heart Rate Elevations							
Placebo	284	8.77 (1.70)	9.57 (1.84)	0.80 (1.70)	0.83 (0.11)	<0.0001	--
QNEXA Low	65	8.36 (1.46)	9.14 (1.71)	0.78 (1.57)	0.69 (0.21)	0.0010	0.5376
QNEXA Mid	132	8.99 (1.77)	9.42 (1.68)	0.44 (1.94)	0.54 (0.16)	0.0006	0.0798
QNEXA Top	488	8.77 (1.73)	9.29 (1.68)	0.52 (1.69)	0.55 (0.09)	<0.0001	0.0118
Subjects Without Heart Rate Elevations							
Placebo	1,247	9.25 (1.50)	8.88 (1.52)	-0.37 (1.59)	-0.42 (0.06)	<0.0001	--
QNEXA Low	169	9.06 (1.41)	8.63 (1.35)	-0.43 (1.39)	-0.55 (0.12)	<0.0001	0.2580
QNEXA Mid	356	9.38 (1.50)	8.80 (1.58)	-0.58 (1.56)	-0.58 (0.09)	<0.0001	0.0561
QNEXA Top	1,063	9.30 (1.48)	8.79 (1.42)	-0.51 (1.59)	-0.53 (0.06)	<0.0001	0.0478
Subjects With Hypertension at Baseline							
Placebo	616	9.66 (1.65)	9.28 (1.69)	-0.39 (1.79)	-0.34 (0.08)	<0.0001	--
QNEXA Low	33	9.76 (1.99)	9.22 (1.53)	-0.54 (1.76)	-0.39 (0.28)	0.1701	0.8597
QNEXA Mid	256	9.56 (1.64)	9.19 (1.68)	-0.37 (1.78)	-0.38 (0.12)	0.0017	0.6816
QNEXA Top	633	9.56 (1.74)	9.09 (1.62)	-0.47 (1.85)	-0.49 (0.08)	<0.0001	0.0796
Subjects Without Hypertension at Baseline							
Placebo	915	8.83 (1.37)	8.83 (1.52)	0.00 (1.57)	0.02 (0.08)	0.8089	
QNEXA Low	201	8.72 (1.30)	8.70 (1.45)	-0.02 (1.49)	-0.02 (0.12)	0.8644	0.7202
QNEXA Mid	232	8.96 (1.47)	8.73 (1.54)	-0.23 (1.66)	-0.18 (0.12)	0.1330	0.0633
QNEXA Top	918	8.84 (1.39)	8.85 (1.44)	0.01 (1.53)	0.04 (0.08)	0.6481	0.7950

a. N is the number of subjects with values at both time points.
b. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
c. Week 56 with LOCF is the last available measurement during the double-blind treatment period.
d. Least-squares mean, SE, and two-sided p-value are from ANCOVA model with treatment and study as fixed effects and baseline as a covariate.
LOCF = last observation carried forward; LS = least squares; QNEXA = fixed-dose combination of phentermine and topiramate; SD = standard deviation; SE = standard error.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Figure 28 presents RPP at baseline and Week 56 for the 1-Year Cohort by treatment group. Larger mean reductions in RPP were observed at Week 56 in each QNEXA group than in the placebo group, though none of the comparisons were statistically significant.

Figure 28. Rate-Pressure Product at Baseline and Week 56 (Safety Set, 1-Year Cohort)



* = significant change from baseline within treatment group.
Comparisons of QNEXA groups to placebo were not significant.
QNEXA = fixed-dose combination of phentermine and topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

5.3.2 Subgroup Analysis of Rate-Pressure Product

Rate-pressure product was also assessed in the following subgroups: age (<60 years, ≥60 years), gender (male, female), race (Black, non-Black), BMI (<40 kg/m^2, ≥40 kg/m^2), diabetes at baseline (with, without), persistent serum bicarbonate reductions during double-blind treatment (with, without), concomitant use of beta blockers (with, without), and weight loss category at Week 56 with LOCF (≤0%, >0% to <5%, ≥5% to <10%, ≥10%). In general, mean reductions in RPP were observed across all treatment groups in each subgroup.

5.4 Predictive Indices for Major Cardiovascular Events

5.4.1 Cooper Clinic Mortality Risk Index

Another method used to evaluate whether or not the specific drug effects on heart rate negatively influenced the risk of major adverse outcomes was to use the algorithm defined in the development of the Cooper Clinic Mortality Risk Index. This algorithm looks simultaneously at factors including age, heart rate, blood pressure, diabetic status, smoking status, and BMI. As the algorithm was validated in a population that consisted of only men, results in **Table 45** show Cooper Clinic Total Mortality Risk Index scores in male subjects treated in clinical studies for PHEN/TPM. These results show a dose-related reduction in mortality risk index scores that was statistically significant for the QNEXA Mid dose and QNEXA Top dose groups. Between-treatment comparisons showed a significantly greater reduction in mortality risk in the QNEXA Top dose group compared to the placebo group,

despite the fact that QNEXA Top dose was associated with the largest increase in heart rate. These results suggest that, according to this algorithm for assessing the risk of 15-year mortality, the small effects of QNEXA to increase heart rate are more than offset by beneficial effects on blood pressure, weight, and diabetic status, and that the overall effects of QNEXA are beneficial, as opposed to detrimental.

Table 45. Change From Baseline and Treatment Comparisons for Cooper Clinic Mortality Risk Index in Male Subjects – 1-Year Cohort

Treatment	n [1]	Baseline [2] Mean (SD)	Week 56 With LOCF [3] Mean (SD)	Change [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	375	13.5 (10.71)	13.4 (10.82)	-0.05 (5.87)	-0.18 (0.33)	0.5945
QNEXA Low dose	40	11.4 (11.18)	11.1 (9.92)	-0.36 (4.44)	-0.45 (0.95)	0.6356
QNEXA Mid dose	147	14.6 (10.58)	13.5 (11.15)	-1.09 (6.48)	-1.12 (0.54)	0.0379
QNEXA Top dose	385	13.1 (10.78)	12.0 (10.28)	-1.07 (6.22)	-1.26 (0.33)	0.0001
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				LS Mean (SE)	95% CI	P-value
QNEXA Top dose (Tmt 1) vs. Placebo (Tmt 2)				-1.08 (0.42)	(-1.91 , -0.26)	0.0101
QNEXA Mid dose (Tmt 1) vs. Placebo (Tmt 2)				-0.95 (0.57)	(-2.07 , 0.18)	0.0994
QNEXA Low dose (Tmt 1) vs. Placebo (Tmt 2)				-0.27 (1.04)	(-2.31 , 1.76)	0.7923

1. n is the number of subjects with values at both time points.
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
3. Week 56 with LOCF is the last available measurement during the double-blind treatment period.
4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment, gender, and diabetic status as fixed effects and baseline as a covariate.

CI = confidence interval; LOCF = last observation carried forward; LS = least squares; QNEXA = VI-0521 fixed-dose combination of phentermine and topiramate; SD = standard deviation; SE = standard error; Tmt = treatment
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

While this algorithm was validated in a population that contained only male subjects, applying it to female subjects treated in clinical studies for QNEXA shows a similar pattern of decreasing risk with increasing dose of PHEN/TPM, which is statistically significant. It is noteworthy that increases in heart rate with QNEXA treatment were, if anything, more pronounced in female subjects than in male subjects. Since epidemiological studies have demonstrated that increased heart rate is more strongly tied to increased cardiac morbidity and mortality in men than in women, this model may in fact, underestimate the potential benefits of treatment in women.

5.4.2 Framingham Risk 10-Year Risk Assessment – Study OB-303

Table 46 presents the results for change in Framingham 10-year risk from baseline to Week 56 with LOCF and the corresponding treatment comparisons for subjects in study OB-303. The Framingham risk score estimates 10-year risk for developing coronary heart disease. The risk factors included in the Framingham calculation are age, gender, total cholesterol, high density lipoprotein cholesterol (HDL-C), SBP, treatment for hypertension, and smoking status. The LS mean change in the Framingham 10-year risk score from baseline to Week 56 with LOCF was -0.0 for the placebo group, -0.5 for the QNEXA Mid dose group, and -0.7 for the QNEXA Top dose group. For the QNEXA treatment groups, the LS mean

change in the Framingham 10-year risk score from baseline was statistically significant (p≤0.0011).

The difference in LS mean change in the Framingham 10-year risk score between QNEXA Top dose and placebo was statistically significant (-0.7; p<0.0001). The difference in LS mean change in the Framingham 10-year risk score between QNEXA Mid dose and placebo was statistically significant (-0.5; p=0.0052).

Table 46. Change in Framingham 10-Year Risk Assessment From Baseline to Week 56 With LOCF and Treatment Comparisons – Intent-to-Treat Set

Treatment	n [1]	Baseline [2] Mean (SD)	Week 56 With LOCF [3] Mean (SD)	Change [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	685	4.9 (5.52)	4.6 (5.24)	-0.3 (2.74)	-0.0 (0.12)	0.8863
QNEXA Mid dose	403	4.7 (5.84)	4.0 (5.18)	-0.7 (3.29)	-0.5 (0.15)	0.0011
QNEXA High dose	799	4.7 (5.78)	3.8 (4.86)	-1.0 (3.17)	-0.7 (0.11)	<0.0001
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				LS Mean (SE)	95% CI	P-value
QNEXA High dose (Tmt 1) vs. Placebo (Tmt 2)				-0.7 (0.14)	(-1.0 , -0.4)	<0.0001
QNEXA Mid dose (Tmt 1) vs. Placebo (Tmt 2)				-0.5 (0.17)	(-0.8 , -0.1)	0.0052

1. n is the number of subjects with values at both time points.
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.
3. Week 56 with LOCF is the last available measurement during the double-blind treatment period.
4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment, gender, and diabetic status as fixed effects and baseline as a covariate.

CI = confidence interval; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error; Tmt = treatment
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

5.5 Major Cardiovascular Event Analysis

This section presents an overview of the incidence rates from the QNEXA Phase 3 program for various composite cardiac endpoints with the understanding that too few events were observed to render any definitive conclusions. Case report summaries of MACE events which occurred in the Phase 3 QNEXA program are discussed in **Appendix 5**.

Concerns regarding the effects of previous obesity pharmacotherapies on cardiovascular outcomes have been recently considered by FDA and discussed by this committee. Those concerns, coupled with evidence of only limited weightloss benefit, ultimately led to the market withdrawal of Meridia (siburtamine) in 2010. Cardiovascular outcomes of long-term treatment with sibutramine were studied in the Sibutramine Cardiovascular Outcomes (SCOUT) trial. Following a 6-week lead-in period during which mean weight loss in the sibutramine group was 2.6 kg, subjects in the sibutramine group lost a mean of an additional 1.7 kg during the 3.4 years of treatment. FDA's analysis of SCOUT (presented to EMDAC on September 15, 2010) found that treatment with sibutramine was associated with an increase in both systolic and diastolic blood pressure of 1−3 mmHg and an increase in heart rate of 3-5 bpm. Sibutramine was associated with an increased risk of a primary outcome cardiovascular event of 16% (HR, 1.16; (5% CI, 1.03−1.31).

Perhaps based in part on this experience, the QNEXA Complete Response Letter ("CRL") requested that VIVUS "[p]rovide evidence that the elevations in heart rate associated with phentermine/topiramate do not increase the risk for major adverse cardiovascular events."

Incidence rates for a series of composite endpoints, defined by progressively broader inclusion of event terms as listed below, were determined. Definitions for each of these endpoints are as follows:

- Cardiovascular Death, MI, and Stroke;
- Jupiter major adverse cardiovascular events (MACE): Cardiovascular Death, MI, Stroke, Coronary Revascularization, and Unstable Angina;
- FDA MACE: Cardiovascular Death, MI, Stroke, Coronary Revascularization, Unstable Angina, and Congestive Heart Failure;
- Modified FDA MACE: Cardiovascular Death, Acute Coronary Syndrome (Non-fatal MI and Unstable Angina), Cerebrovascular Events (Non-fatal Stroke and Transient Ischemic Attack), Coronary Revascularization, Hospitalization for Heart Failure, Stent Thrombosis, Hospitalization for Other Cardiovascular Causes, Carotid Artery Revascularization, Peripheral Vascular Revascularization, Lower Extremity Amputation, Hospitalization for Cardiac Arrhythmia;
- Cardiac Disorders System Organ Class (SOC) SAEs: All SAE preferred terms mapping to the Medical Dictionary for Regulatory Activities (MedDRA) Cardiac Disorders SOC;
- Cardiovascular and Neurovascular SAEs: All SAE preferred terms mapping to the MedDRA Cardiac Disorders SOC, and SAEs with preferred terms of deep vein thrombosis, hypertension, hypotension, brain stem infarction, cerebral infarction, cerebrovascular accident, haemorrhorage intracranial, transient ischemic attack, chest pain, non-cardiac chest pain, and pulmonary embolism.

Of these endpoints, the first three are commonly used and well-accepted composites for the evaluation of cardiovascular morbidity and mortality and the fourth is recommended by FDA guidance. However, because the population treated in the QNEXA program was selected primarily to be representative of patients who would seek treatments for obesity; these subjects were predominantly female, and considerably younger than the populations typically targeted for cardiac outcomes studies. Consequently, the number of observed events using the first three (more restrictive) definitions listed above was lower than needed for a robust analysis of these outcomes. The remaining three endpoints are intended to capture a greater number of events to further evaluate the existence of any signal, recognizing that some of the captured events are less serious than those used in the first three composite endpoints. A by-subject listing of terms captured by these endpoint definitions, and where applicable, adjudication of terms into MACE definitions, is provided in **Table A5.1** of Appendix 5. Narratives for subjects who experienced MACE events are presented in **Appendix 5**.

For each of the categories of outcomes evaluated, annualized incidence rates, hazard ratios (QNEXA versus placebo) determined by Cox proportional hazard analysis, and 95% confidence intervals (CI) are presented in **Table 47**. **Figure 29** presents a forest plot for the hazard ratio and 95% confidence interval for the comparison of QNEXA total versus placebo for the incidence of cardiovascular events in each of the categories evaluated. Also presented in **Figure 29** are the numbers of events within each category for the placebo and QNEXA total groups.

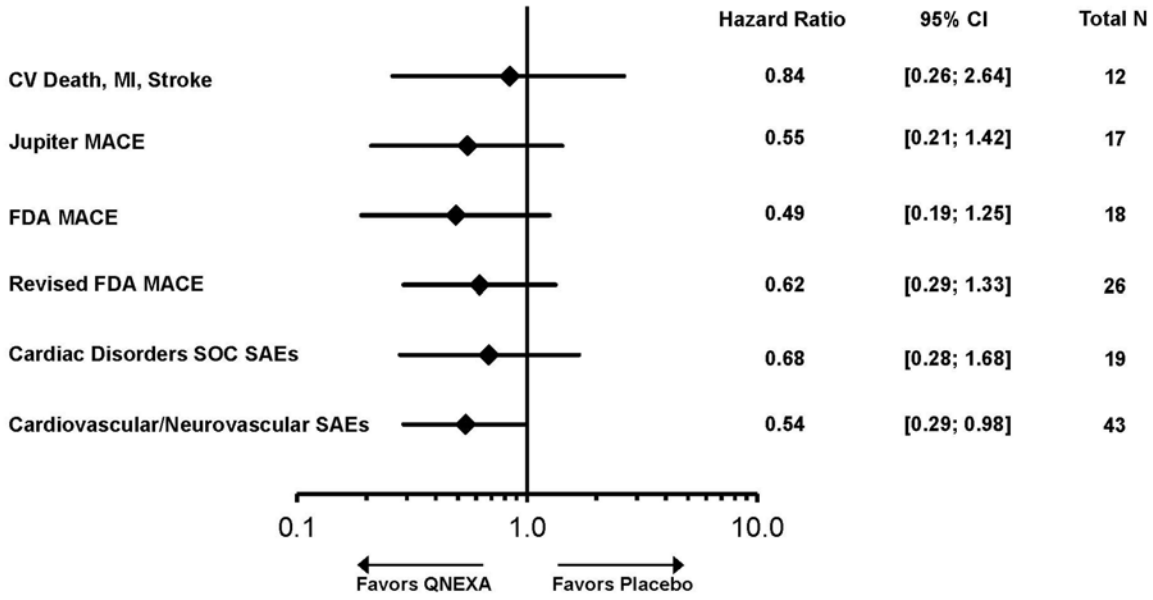
Across the different definitions of outcomes evaluated, hazard ratios (QNEXA versus placebo) were all <1.0 and relatively consistent, ranging from 0.49 for the FDA MACE endpoint to 0.84 for the endpoint of cardiovascular death, MI, and stroke. Because of the narrow definition and small number of events (7 subjects treated with QNEXA and 5 subjects treated with placebo) for the endpoint of cardiovascular death, MI and stroke, the 95% confidence interval of the hazard ratio had an upper bound of 2.64. For each of the other composite outcome endpoints, the 95% confidence interval of the hazard ratio had an upper bound ranging from 0.98 for the broadest definition and the largest number of subjects with events (23 subjects treated with placebo and 20 subjects treated with QNEXA), to 1.68 for the Cardiac Disorders SOC.

Table 47. Annualized Incidence Rates for Cardiovascular Event Outcomes, Hazard Ratios versus Placebo, and 95% Confidence Intervals – (Safety Set)

	Annualized Incidence Rate						
Event Category	**Placebo (N=1,742)**	**QNEXA Low (N=240)**	**QNEXA Mid (N=604)**	**QNEXA Top (N=1,737)**	**QNEXA Total (N=2,581)**	**HR[a]**	**95% CI**
CV death, MI, Stroke	0.3	0.5	0.3	0.2	0.3	0.84	0.26, 2.64
Jupiter MACE	0.6	0.5	0.3	0.3	0.3	0.55	0.21, 1.42
FDA MACE	0.6	0.5	0.3	0.3	0.3	0.49	0.19, 1.25
Modifed FDA MACE	0.8	0.5	0.6	0.5	0.5	0.62	0.29, 1.33
Cardiac Disorders SOC SAEs	0.6	0.5	0.6	0.3	0.4	0.68	0.28, 1.68
Cardiovascular/ Neurovascular SAEs	1.5	1.0	0.9	0.7	0.8	0.54	0.29, 0.98

a. Hazard ratio is from a univariate Cox proportional hazards regression analysis comparing QNEXA total to placebo.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; QNEXA = fixed-dose combination of phentermine and topiramate; SAE = serious adverse event; SOC = system organ class.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

Figure 29. Relative Risk of Major Cardiovascular Events – (Safety Set)



These analyses do not indicate that treatment with QNEXA increases the risk for serious cardiovascular events. In the absence of an increased risk signal, it becomes much more difficult to assess the potential for any increase in heart rate to increase the risk for these events.

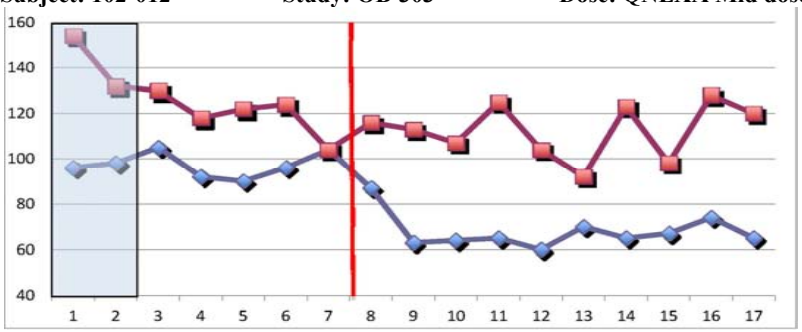
One way of evaluating this potential is to look at the temporal pattern of heart rate and systolic blood pressure in individual subjects who experienced events, and to assess the potential relationship between any changes in heart rate and the occurrence of these events. Examination of heart rate and blood pressure data from individual subjects with a major CV event demonstrates that there is no clear pattern of increase in heart rate or blood pressure in conjunction with the occurrence of the major CV event. The majority of these subjects also had baseline heart rates that were well below the average for this population. Overall, the on-treatment heart rates appear to be more closely related to baseline heart rate than any other factor.

Presented in **Figure 30** are graphs of SBP and heart rate over time for the 11 subjects reporting cardiovascular death, MI, or urgent coronary revascularization during study treatment. Study visit is plotted on the horizontal axis where Visit 1 is the Screening visit, Visit 2 is the baseline visit when randomization occurred and study medication was first dispensed, Visit 3 corresponds to Week 2, Visit 4 corresponds to Week 4, and all subsequent visits occurred at 4 week intervals. Time of the event is indicated by the vertical line. For the 6 myocardial infarctions, the mean change in heart rate from baseline to the last visit prior to the event was -1.5 bpm and the mean change in SBP from baseline to the last visit prior to the event was -12.3 mmHg. Similarly for the 1 death and 4 revascularization events, the mean change in heart rate from baseline to the last visit prior to the event was -1.4 bpm and the mean change in SBP from baseline to the last visit prior to the event was 1.0 mmHg. No

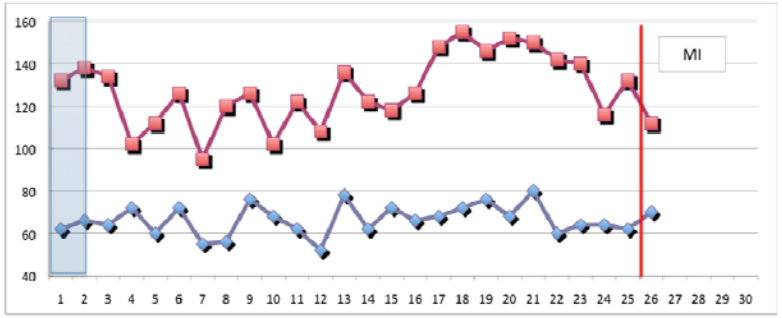
evidence for a temporal pattern of the events, nor of a causal role for changes in heart rate associated with study drug, has been observed.

Figure 30. Systolic Blood Pressure and Heart Rate of Subjects Reporting Cardiovascular Death, MI, or Urgent Coronary Revascularization During Study Treatment

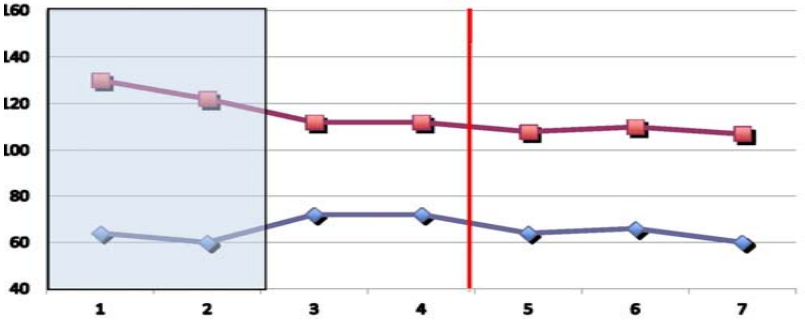
Subject: 102-012 Study: OB-303 Dose: QNEXA Mid dose



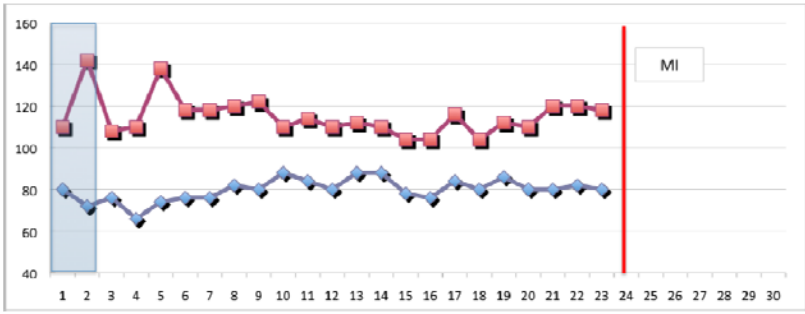
Subject: 131-059 Study: OB-305 Dose: QNEXA Mid dose



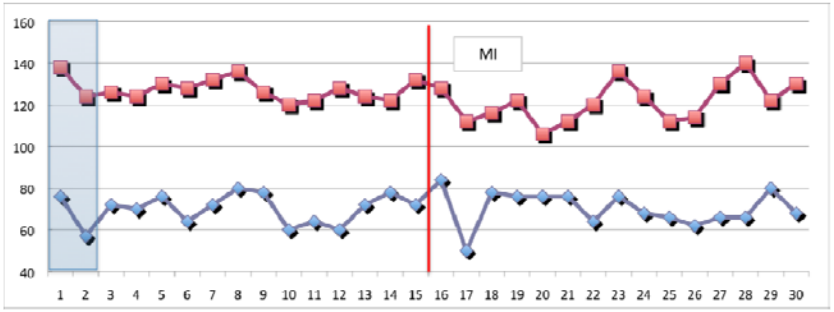
Subject: 116-036 Study: OB-302 Dose: QNEXA Low dose



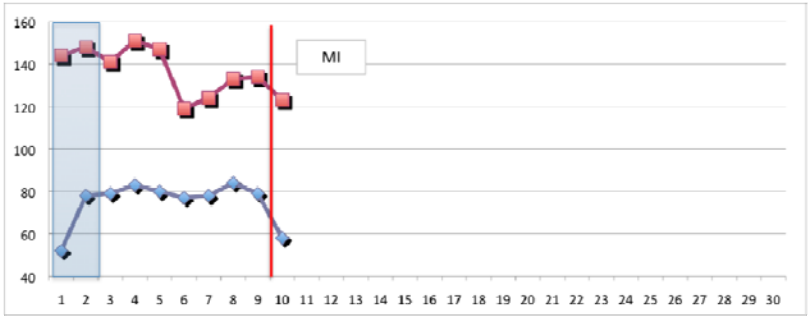
Subject: 178-121 Study: OB-305 Dose: QNEXA Top dose



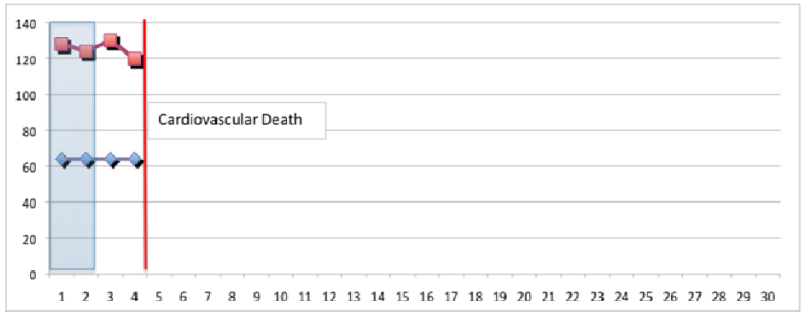
Subject: 131-042 Study: OB-303/305 Dose: QNEXA Top dose



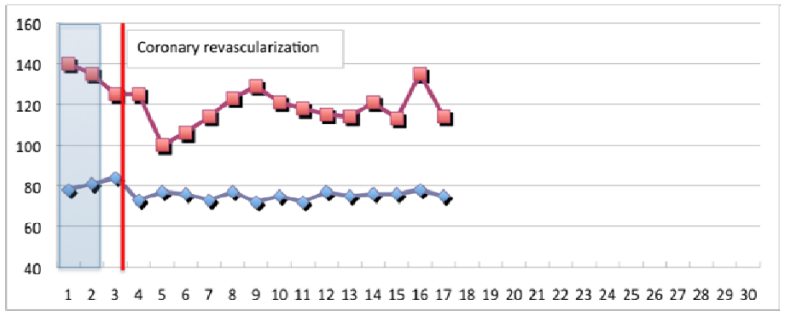
Subject: 188-052 Study: OB-303 Dose: QNEXA Top dose



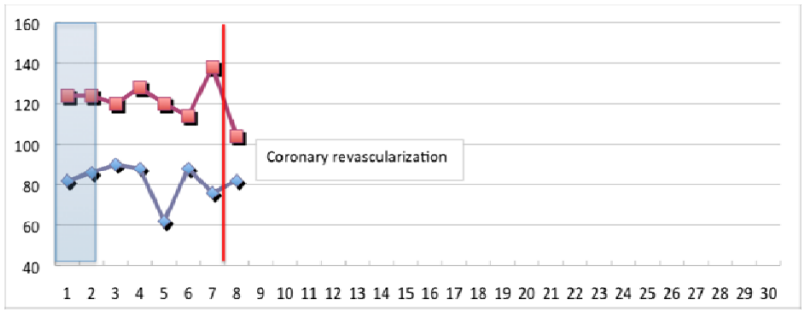
Subject: 143-037 **Study: OB-303** **Dose: Placebo**



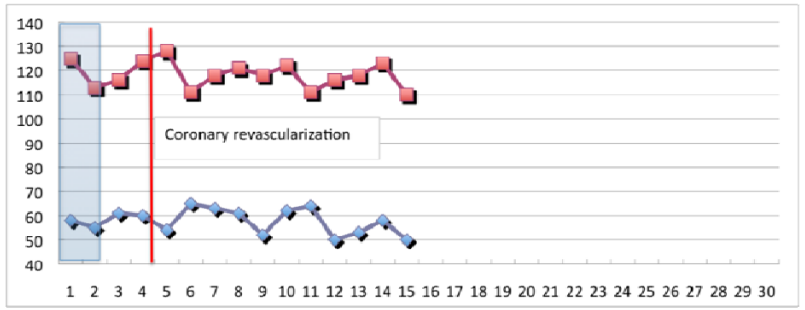
Subject: 108-043 **Study: OB-303** **Dose: Placebo**



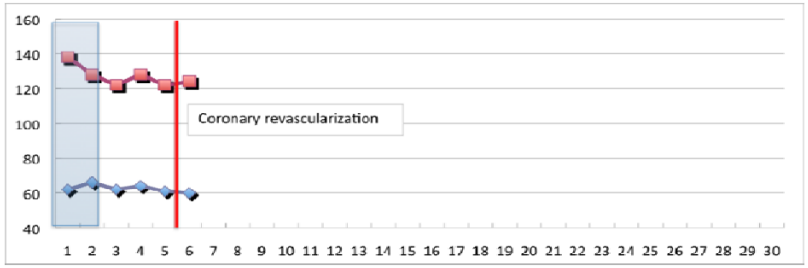
Subject: 130-050 **Study: OB-303** **Dose: Placebo**



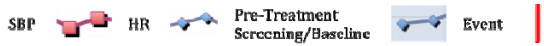
Subject: 151-079 **Study: OB-303** **Dose: Placebo**



Subject: 193-032 **Study: OB-303** **Dose: Placebo**



All coronary revascularizations were performed on an emergency basis.
X axis represents study visit; initial visit shown is Screening (Visit 1); Baseline is Visit 2.



Analyses of major adverse cardiovascular events within the clinical program using multiple accepted criteria confirm that treatment with QNEXA is not associated with a signal for an increased frequency of major cardiovascular events compared to placebo. In patients that experienced major events, there does not appear to be any consistent pattern of heart rate increases preceding these events, and when the overall effects of QNEXA are evaluated with validated risk models that include heart rate, the beneficial effects of QNEXA on BMI, blood pressure, and diabetic status, clearly outweigh potential adverse effects on heart rate.

Considering the overall absence of excess major adverse cardiovascular events in subjects in this program who received treatment with QNEXA, the lack of a direct relationship between major adverse cardiovascular events and heart rate changes, and the beneficial effects of QNEXA in models of cardiovascular risk that include heart rate, it does not appear that the small heart rate increase observed with QNEXA treatment can be associated with an increased risk for major cardiovascular events.

5.6 Cardiovascular Discussion and Conclusions

QNEXA has a complex cardiovascular pharmacology profile that is a result of the two agents utilized in this combination: topiramate, which acts through several centrally mediated mechanisms and has mild diuretic effects, and phentermine, which acts through hypothalamic norepinephrine release. Evidence from 6-month studies with phentermine monotherapy demonstrate consistent lowering effects on blood pressure with neutral to small increases in heart rate. In a retrospective analysis by Hendricks (2010), long-term phentermine-treated patients maintained a clinically meaningful weight loss for as long as 8 years. Phentermine had minimal effect on pulse and declines in blood pressure depended on initial blood pressure category and weight loss. A summary of the phentermine literature and QNEXA clinical trial experience supports the general observation that treatment with phentermine monotherapy leads to weight loss with a reduction of blood pressure that is of greater magnitude in the presence of hypertension at baseline (Hendricks 2011). The cardiovascular effects of QNEXA are further differentiated by the action of topiramate, which has been shown to significantly lower blood pressure and decrease heart rate.

Heart rate is highly variable, both across populations and within individuals. Although "normal" heart rate is traditionally defined as 60 to 100 bpm, large epidemiologic studies have demonstrated that the mean adult resting heart rate is approximately 70 bpm, and that 95% of the population would fall within a range of about 50 to 90 bpm. There are several factors that have been linked with the presence of an elevated resting heart rate, including sedentary lifestyle, age, hypertension, diabetes, and obesity. Several classes of medications have also been associated with either modulation of, or increase of, heart rate.

A review of available published data supports the conclusion that the risk of major cardiovascular events associated with an increase in heart rate may only be important when comparisons are made between groups with a low baseline heart rate and those with a moderate to high resting heart rate (Kannel 1987; Theobald 2007; Tverdal 2008; Benetos 1999; Gillman 1993). In the case of patients with established coronary disease or previous myocardial infarction (MI), the evidence of risk associated with elevated resting heart rate or categorical increases in heart rate is observed in most, but not all cardiovascular

outcome studies (King 2006; Diaz 2005; Fox 2008; Okin 2010; Boersma 2000; Heidland 2001). Furthermore, in the case of a treatment that positively addresses other independent cardiovascular risk factors such as blood pressure, the risk of heart rate increases may be mitigated (Janssen 2005). Thus, the risk posed by small increases in heart rate in the presence of an overall improvement in metabolic disease status would not be expected to have the same adverse impact on risk as heart rate changes that come in the absence of metabolic disease benefit.

The relationship between blood pressure and the risk of cardiovascular events is continuous, consistent, and independent of other risk factors (Lewington 2002). A meta-analysis of 61 prospective, observational studies in 1 million adults indicates that for every 2 mmHg decrease in systolic blood pressure there is an associated 7% reduction in risk of cardiovascular disease (CVD) mortality and a 10% reduction in risk of stroke mortality (Lewington 2002). Thus, the risk posed by transient or small increases in heart rate in the presence of an overall improvement in metabolic disease status would not be expected to have the same adverse impact on risk as heart rate changes that come in the absence of metabolic disease benefit.

In an effort to quantify the contributions of various intrinsic and extrinsic variables on cardiovascular risk, a variety of models have been developed to predict risk of mortality and major cardiovascular events (National Heart and Blood Institute 2010; Cooney 2010; Ridker 2007; Janssen 2005). Development of these models has evolved over 50 years to include dozens of potential risk factors; however, heart rate has not been included in the majority of widely used models. The Cooper Clinic Mortality Risk Index for men does incorporate heart rate and it accords equal weighting to blood pressure and assigns risk only for an absolute heart rate >80 bpm (Janssen 2005).

Intensive assessment of numerous cardiovascular risk factors has demonstrated that the weight loss observed with QNEXA treatment is associated with favorable effects on hypertension, dyslipidemia, and diabetes. Although these improvements were observed across the broader population, the small heart rate increases were driven to a large degree by subjects with a low baseline heart rate.

Overall, the QNEXA program has included over 4300 subjects treated from 6 months to 2 years. The change in heart rate associated with the use of QNEXA is small (increases between 0.6 and 1.6 bpm at study exit compared with baseline) depending on dose. There was no subgroup identified that appeared to demonstrate a greater risk for adverse effects on HR compared to the general population. The change in heart rate was accompanied in almost all subjects by a similar or slightly greater reduction in blood pressure, resulting in no change between QNEXA- and placebo-treated subjects in the mean rate-pressure product, an indicator of cardiac oxygen demand. Moreover, increases in heart rate are not generally observed in subjects with elevated baseline heart rates.

Detailed analysis of serious adverse events in the QNEXA program by various groupings, while limited by small numbers of events, showed no signal of increased adverse outcomes in cardiovascular or neurovascular events. In addition, the temporal pattern of change in heart rate and blood pressure in 43 subjects who experienced serious cardiac or neurovascular

events did not reveal an association of these SAEs to antecedent changes in heart rate or blood pressure.

In summary, based on the detailed analyses presented, the small heart rate elevations associated with QNEXA do not increase the risk of major cardiovascular events. Treatment with QNEXA has demonstrated durable weight loss of greater than 10% at the end of two years. When used as labeled, QNEXA represents a safe and effective therapy for the management of obesity and has the promise to be a valuable adjunct to diet and exercise for patients with this disorder. Although the data in the investigational program involving more than 4,300 subjects support a favorable risk:benefit profile for QNEXA in the indicated population, VIVUS has proposed a definitive, long-term, post-approval outcomes study to refine our understanding of the long-term risks and benefits of QNEXA (**Appendix 4**).

6 REVIEW OF TERATOGENICITY INFORMATION

During the initial review of the NDA for QNEXA, FDA raised a concern about the teratogenic potential of topiramate based on data from the North American Antiepileptic Pregnancy Registry (NAAPR) (Hernandez-Diaz 2010). At that time, the prevalence of major congenital malformations (MCMs) in the NAAPR was 3.8% (11/289 exposed pregnancies) with a relative risk of 2.8 (95% CI, 1.0–8.1) compared to untreated controls. Four of the 11 MCMs were oral cleft (OC), two of which were isolated. The prevalence of isolated OC (2/289) of 0.69% was roughly 10-fold higher than the background prevalence cited as 0.07%. Dosage information has not been provided by the NAAPR. Based largely on these data, the QNEXA CRL requested that VIVUS "[p]rovide a comprehensive assessment of topiramate's and phentermine/topiramate's teratogenic potential." The discussion below is based on various epidemiologic and registry data regarding topiramate. A summary of non-clinical teratogenicity studies is provided in **Appendix 7**.

6.1 Pregnancy Category and Other Prescribing Information

FDA regulations require that prescribing information for all drugs identify a pregnancy category based on risks of the drug to unborn fetuses when taken by the mother. The permissible categories are:

- Pregnancy Category A: adequate and well-controlled trials in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters);

- Pregnancy Category B: animal reproductive studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled trials in pregnant women;

- Pregnancy Category C: animal reproductive studies have shown an adverse effect on the fetus, there are no adequate and well-controlled trials in pregnant women, and the benefits of the drug in pregnant women may be acceptable despite the potential risks;

- Pregnancy Category D: there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from use of the drug in pregnant women may be acceptable despite the potential risks; and

- Pregnancy Category X: studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.

FDA has proposed to amend its regulations to eliminate these categories and instead require that labeling include a summary of the risks of using the drug during pregnancy and a discussion of the data supporting that summary including relevant clinical data to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy. In the absence of finalized revised regulations or FDA guidance in this area, the proposed QNEXA prescribing information is based on the existing Pregnancy Categories as discussed below. VIVUS, however, intends to work with FDA to implement more informative labeling consistent with evolving FDA standards.

The prescribing information for approved phentermine products carries either a Pregnancy Category C designation or a Pregnancy Category X designation, for more recent approvals. Topiramate prescribing information carries a Pregnancy Category D designation indicating that despite evidence of fetal risk, the use of the drug may still be acceptable in pregnant women based on its potential benefits in epilepsy and migraine prevention. Thus, despite data from pregnancy registries indicating that newborn infants who were exposed to topiramate *in utero* have an increased risk for OC, and data from multiple species of pregnant animals indicating that topiramate causes structural malformations, including craniofacial defects, and reduced fetal weights, the use of topiramate is not contraindicated during pregnancy in epileptic patients or migraneurs, even though "the risks of oral clefts to the fetus occur during the first trimester of pregnancy before many women know they are pregnant."

VIVUS understands that FDA's current policy is that all obesity drugs should be labeled as Pregnancy Category X because weight loss itself offers no potential benefit to a pregnant woman and may result in fetal harm. As such, VIVUS has proposed that QNEXA be labeled as Pregnancy Category X.

6.2 Topiramate Registries and Observational Studies

6.2.1 The North American Anti-epileptic Pregnancy Registry (NAAPR)

The NAAPR primarily enrolls pregnant epileptics from the United States and Canada. Recruitment is through self-enrollment of women by calling a toll-free number to register. There are two phone interview follow-ups, at 7 months of pregnancy and 8–12 weeks after estimated date of delivery. Medical records are also reviewed if there is written consent from the mother (which is granted by about 60% of the enrolled women) (Tomson 2010). Only a small percentage of pregnancies of women with epilepsy on anti-epileptic drugs (AED) treatment in North America is captured by the registry, and there may be regional differences

in ascertainment rate. NAAPR utilizes internal as well as external comparison groups of non-epileptic women who were not exposed to AEDs.

In the first 372 enrolled internal controls, the malformation rate at birth was 1.3% (Hernandez-Diaz 2010). In the external control group taken from the Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston, the malformation rate was 1.6% after excluding infants with known genetic disorders and chromosomal abnormalities (Nelson 1989; Peller 2004). These rates of major malformation in the external (1.6%) and internal (1.3%) control groups are significantly lower than those reported by the March of Dimes (4%) or by the Center for Disease Control and Prevention (CDC) (3%) in the general population. The basis of the discrepancy in reported rates of malformation is unknown.

In 2009, the NAAPR reported a prevalence rate of MCM of 4.1% for topiramate (**Table 48**) (Holmes 2009). The authors cautioned that the malformations were eight separate and common birth defects that did not show an increase for any specific abnormality. TPM dosing information was not provided with this report. As pregnancy enrollment increased in the NAAPR, the apparent prevalence rate of MCM associated with topiramate decreased to 3.8% (Hernandez-Diaz 2010). The most recent results from the NAAPR include updated rates of MCMs observed with various AEDs, 3.4% (11/321) for topiramate (Hernandez-Diaz 2011). This study also used MCM rates associated with lamotrigine as a reference group for all other AEDs. Compared to lamotrigine, the relative risk of MCMs was 1.8 (0.9–3.6) for topiramate and 4/321 infants exposed to topiramate (1.3%) had oral clefts.

Table 48. Summary of Major Malformations Following in Utero Exposure to TPM Monotherapy Reported by the NAAPR

Reference	Compound or Controls	Population or Indication	Total Malformations	Enrolled Pregnancies	Prevalence of Malformations	95% CI Intervals
Holmes, 2009	TPM	Mainly epileptic (90%)	8	197	4.1 %	1.9–7.6 %
Hernandez-Diaz, 2010	TPM	Mainly epileptic (90%)	11	289	3.8 %	NR
Hernandez-Diaz, 2011	TPM	Mainly epileptic (90%)	11	321	3.4%	1.9–6.0
Hernandez-Diaz, 2010	Internal control[a]	Non-epileptic	5	372	1.3%	NR
Holmes, 2009	External control[b]	Non-epileptic	1,119	69,277	1.6%	1.5–1.7 %

a. Internal controls of friends and family members of eligible and enrolled participants who are not taking AEDs.
b. Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston.
CI = confidence interval; NAAPR = North American Anti-epileptic Pregnancy Registry; NR = not reported; TPM = topiramate.

In 2010, the NAAPR also reported two cases of isolated cleft lip out of 289 total pregnancies which is an apparent prevalence rate of 0.7% and an apparent increase when compared to an expected prevalence of isolated cleft lip of around 0.07%. NAAPR itself cautioned that the overall number of pregnancies was too few and further exploration would be required to

establish an association between TPM monotherapy and risk of major malformations as there could be an imbalance of risk factors among anti-epileptic drug users.

6.2.2 Other Pregnancy Registries

Data from the UK Epilepsy and Pregnancy Register included informative outcomes from 83 births after maternal exposure to topiramate (Morrow 2006; Hunt 2008; Kennedy 2010). There were three MCMs within this group, representing a prevalence of 3.6%. Two of these three involved OC: one cleft palate and bilateral cleft lip (topiramate 200 mg/d) and one cleft lip and palate (600 mg/d). The remaining malformation was a case of hypospadias (400 mg/d).

Data from topiramate exposure during pregnancy were also reported by the Israeli Teratogen Information Service (Ornoy 2008). Outcomes data included 52 pregnancies and 41 liveborn infants exposed to topiramate in utero, either as monotherapy (29) or polytherapy (23). Four MCMs were identified among the 41 liveborn infants (9.8% prevalence). Two of these were genetic in origin (1 DiGeorge syndrome and 1 Prader-Willi syndrome). The remaining 2 apparently non-genetic cases (4.9%) included 1 instance of pulmonary artery stenosis (topiramate dosage 475 mg daily) and 1 case involving multiple brain cysts (topiramate 50 mg daily along with valproic acid 800 mg/d and clonazepam 1 mg/d).

As of the most recent publication of results from the Australian Pregnancy Registry, there were data on 15 births with exposure to topiramate monotherapy during the first trimester, none of which resulted in major congenital malformations (Vajda 2007).

6.2.3 Meta-analysis of TPM Pregnancy Registry Data

A meta-analysis of 448 pregnancies (monotherapy TPM) pooled the data from the four existing registries described above (Australia, Israel, UK, and North America; **Table 49**), as well as information on control groups (**Table 50**).

Table 49. Experience with TPM Monotherapy during Pregnancy – Meta-Analysis

Source	Malformations/ Information Outcomes	Percentage (95% CI)	Author, Date
Israeli Teratogen Information Service	1/29	3.4	Ornoy 2008
UK Epilepsy and Pregnancy Register	3/83	3.6	Kennedy 2010
North American AED and Pregnancy Registry	11/321*	3.4	Hernandez-Diaz 2011
Australian AED Registry	0/15	0	Vajda 2007
Total	15/448	3.3% (2.0–5.5%)	

* number of enrolled pregnancies
AED = anti-epileptic drug; CI = confidence interval; UK = United Kingdom; TPM = topiramate.

Table 50. Malformation Rates in Untreated Epileptics – Meta-Analysis

Source	Malformations/ Informative Outcomes	Percentage (95% CI)
Fried 2004	13/400	3.3 (1.9, 5.5)
Morrow 2006	8/227	3.5 (1.8, 6.8)
Vajda 2007	3/83	3.6 (1.2, 10.1)
Total	24/710	3.4 (2.3, 5.0)

CI = confidence interval.

The point estimate of relative risk for major malformations was 0.99 (95% CI, 0.53–1.86) indicated no significant difference between groups (**Table 51**). While this meta-analysis is limited by its focus only on overall MCMs as opposed to specific malformations, it does include a control group comprised of untreated epileptic women as contrasted with the NAAPR control cohorts who did not follow the same selection process as treated patients and were not epileptic.

Table 51. Relative Risk for Malformation Rates for TPM Monotherapy Compared to Non-treated Epileptics – Meta-Analysis

	TPM Treated Epileptics	Untreated Epileptics (Control)
Malformations/Live Births	15/448	24/710
Percentage (95% CI)	3.3% (2.0–5.5%)	3.4 (2.3, 5.0)
Relative risk (95% CI)	0.99 (0.53, 1.86)	

CI = confidence interval; TPM = topiramate.

6.3 Other Retrospective Data

6.3.1 The Danish Population Study

In May of 2011, Danish epidemiologists published results of a large, population-based cohort study of major birth defects associated with first trimester exposure to newer-generation antiepileptic drugs, including topiramate (Molgaard-Nielsen 2011). This study included data from all live births in Denmark (837,795 infants) from January, 1996 through September, 2008. The structure of the Danish healthcare system allowed the investigators to associate individual-level diagnostic codes with prescription data in order to determine exposure to one or more of the study drugs and the prevalence of MCMs in exposed and unexposed cohorts.

There were 49 major malformations among 1532 infants exposed to one of five newer-generation antiepileptic drugs during the first trimester (3.2%) compared to 19,911 of 836,263 infants who were not exposed to an antiepileptic drug (2.4%); a crude prevalence odds ratio (POR) of 1.35 (95% CI, 1.02–1.80). After adjustment for confounders (i.e., exposure to an older-generation antiepileptic drug during the first trimester and diagnosis of epilepsy before

the second trimester), the adjusted POR was 0.99 (95% CI, 0.72–1.36) (**Table 52**). Only 108 infants were exposed to topiramate during the first trimester. There were 5 major malformations among the topiramate-exposed group. The adjusted POR for topiramate was 1.44 (95% CI, 0.58–3.58). Although a small number of infants were exposed to topiramate, the study authors concluded that a relative risk of any major birth defect greater than 3.58 for topiramate can "probably be excluded with some certainty."

Table 52. Association Between First-Trimester Exposure and Major Birth Defects

First Trimester Exposure	No. of Women	No. (%) Birth Defects	Crude POR (95% CI)	Adjusted POR (95% CI)
None	836,263	19,911 (2.4)	1.0 (Reference)	1.0 (Reference)
AED[a]	1532	49 (3.2)	1.35 (1.02–1.80)	0.99 (0.72–1.36)
Topiramate	108	5 (4.6)	1.99 (0.81–4.88)	1.44 (0.58–3.58)

a. lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam.
AED = antiepileptic drug; CI = confidence interval; POR = prevalence odds ratio.

This study also explored the possibility that a particular type of birth defect might be associated with first trimester exposure to one of the five study drugs. Examination of 13 classes of major birth defects by organ system (including orofacial clefts) failed to identify any significantly increased risk for any subgroup of major birth defect.

6.3.2 Data From Case-control Surveillance Programs

Data were evaluated from two large case-control surveillance programs (i.e., the Slone Epidemiology Center Birth Defects Study [BDS, 1997-2009], and the Center for Disease Control's National Birth Defects Prevention Study [NBDPS, 1996-2007]) to evaluate the risk of OC with exposure to topiramate monotherapy during the first trimester of pregnancy (Margulis 2011). There were 10,621 MCM cases, including 785 OC cases, in the BDS and 23,204 MCM cases, including 2,632 OC cases, in the NBDPS. There were 6,986 and 8,451 non-malformed controls from the BDS and NBDPS, respectively. Numbers of cases and controls by drug exposure along with adjusted odds-ratios and 95% confidence intervals are presented in **Table 53**.

Table 53. Adjusted OR and 95% Confidence Intervals for Topiramate versus No AED Exposure by Study

Study		No. of AED	Topiramate	Adjusted OR	(95% CI)
BDS	Control	6,933	2	Reference	
	Total MCM	10,503	5	1.22	(0.19–13.01)
	OC	778	3	10.13	(1.09–129.21)
NBDPS	Control	8,434	4	Reference	
	Total MCM	23,102	10	0.92	(0.26–4.06)
	OC	2,256	4	3.63	(0.66–20.00)
Combined	Control	15,367	6	Reference	
	Total MCM	33,605	15	1.01	(0.37–3.22)
	OC	3,034	7	5.36	(1.49–20.07)

AED = antiepileptic drug; BDS = Slone Epidemiology Center Birth Defects Study; CI = Confidence Interval; NBDPS = Center for Disease Control's National Birth Defects Prevention Study; MCM = major congenital malformation; OC = oral cleft; OR = odds ratio

In sensitivity analyses that further matched, one by one, on folic acid intake, smoking, epilepsy, and other potential confounders, results were not changed meaningfully. These findings suggest that exposure to topiramate monotherapy during the first trimester of pregnancy may be associated with an increased risk of OC, but is not associated with an increased risk for MCM overall.

6.3.3 Wolters – Kluwer Database

This study was a retrospective cohort-control evaluation of OCs and MCMs in offspring of women exposed to topiramate during pregnancy. The study evaluated data from the Wolters Kluwer Pharma Solutions Source® Lx Patient Longitudinal database, which tracks patients' pharmacy and medical claims. Records for all female patients with medical claims relating to child birth from January 2003 to December 2010 were assessed for the occurrence of both pharmacy and medical claims data extending for a period of at least 13 months prior to the index birth for inclusion in the study. From these data, a cohort of women with likely exposure to topiramate during pregnancy, at any dose and regardless of diagnosis, was defined.

The following comparator cohorts were also described:

- Women exposed to other antiepileptic drugs during pregnancy;
- Women with a diagnosis of epilepsy or seizures;
- Women with a diagnosis of migraine (but no diagnosis of epilepsy);
- Women with a diagnosis of migraine (but no diagnosis of epilepsy) and treated during pregnancy with acute and preventative migraine drugs (APMDs); and
- Women with a diagnosis of diabetes (other than gestational).

Infants with chromosomal malformations and women with exposure to known teratogens or valproic acid were excluded.

This study identified 910 mother/infant dyads with topiramate exposure anytime during pregnancy. Prevalence rates for OCs and MCMs are presented in **Table 54**, along with prevalence rates in the various comparator cohorts.

Table 54. Prevalence Rates of OC and MCM in Children Born to Women Exposed to Topiramate Anytime During Pregnancy

	n	Oral Clefts		MCMs	
		Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator	Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator
Topiramate	910	0.22	n/a	3.96	n/a
Other AEDs	4,320	0.23	0.95 (0.21–4.33)	3.38	1.17 (0.82–1.67)
Epilepsy	2,607	0.31	0.72 (0.15–3.37)	4.33	0.91 (0.63–1.32)
Migraine	26,865	0.16	1.41 (0.34–5.80)	3.79	1.05 (0.75–1.45)
Migraine APMD	3,339	0.33	0.67 (0.15–3.00)	3.95	1.00 (0.70–1.44)
Diabetes	13,063	0.26	0.84 (0.20–3.51)	6.58	0.60 (0.43–0.83)

AED = antiepileptic drug; APMD = acute and preventative migraine drugs; CI = confidence interval; MCM = major congenital malformation; OR = oral cleft; RR = relative risk; TPM = topiramate.

Prevalence rates of OC and MCMs in children of women exposed to topiramate during the first trimester of pregnancy are presented in **Table 55**.

The prevalence rate of OC in children born to women exposed to topiramate anytime during pregnancy (0.22%) was within the range seen in the comparator cohorts (0.16% for the migraine cohort, to 0.33% for the migraine APMD cohort). Unadjusted relative risk values for OC frequency ranged from 0.67 for the comparison between the topiramate cohort and the Migraine APMD cohort, to 1.41 for the comparison between the topiramate cohort and the Migraine cohort. For all comparator cohorts, the 95% confidence intervals of the RR of OC compared to topiramate included 1.

The prevalence of MCMs in children of women exposed to topiramate anytime during pregnancy (3.96%) was similar to the corresponding prevalences in the Other AED, Epilepsy, Migraine APMD, and Migraine no APMD cohorts, and significantly less than the prevalence in the Diabetes cohort of 6.58% (RR 0.60: 95% CI, 0.43–0.83).

Table 55. Prevalence Rates of OC and MCM in Children Born to Women Exposed to Topiramate During the First Trimester of Pregnancy

	n	Oral Clefts		MCMs	
		Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator	Prevalence Rate (%)	RR (95% CI) Topiramate vs. Comparator
Topiramate	870	0.23	n/a	4.25	n/a
Other AEDs	3,615	0.17	1.39 (0.28-6.85)	3.21	1.33 (0.92-1.90)
Epilepsy	2,607	0.31	0.75 (0.16-3.52)	4.33	0.98 (0.68-1.41)
Migraine	26,865	0.16	1.47 (0.36-6.06)	3.79	1.12 (0.81-1.55)
Migraine APMD	2,526	0.24	0.95 (0.19-4.68)	4.32	0.99 (0.68-1.42)
Diabetes	13,063	0.26	0.88 (0.21-3.67)	6.58	0.65 (0.47-0.89)

AED = antiepileptic drug; APMD = acute and preventative migraine drugs; CI = confidence interval; MCM = major congenital malformation; OR = oral cleft; RR = relative risk; TPM = topiramate.

Among the 910 women exposed at some time during pregnancy, 870 women were exposed to topiramate specifically during the first trimester. In these women, the prevalence rate of OC was 0.23%, which was within the range seen in the various comparator cohorts (0.16% for the Migraine cohort to 0.31% for the Epilepsy cohort). Unadjusted relative risk values for OC frequency ranged from 0.75 for the comparison between the topiramate cohort and the Epilepsy cohort, to 1.47 for the comparison between the topiramate cohort and the Migraine cohort. For all comparator cohorts, the 95% confidence intervals of the RR of OC compared to topiramate included 1.

For women with first trimester exposure to topiramate, the prevalence rate of MCM was 4.25%, which was comparable to the rates observed in the Other AED, Epilepsy, Migraine APMD, and Migraine no APMD cohorts, and significantly less than the prevalence in the Diabetes cohort of 6.58% (RR 0.65: 95% CI, 0.47–0.89).

6.3.4 FORTRESS

VIVUS and FDA have reached agreement on the key design aspects of a retrospective observational study, now underway, that utilizes existing electronic medical claims healthcare databases to review fetal outcomes, including the incidence of congenital malformations and oral cleft, in the offspring of women who received topiramate during pregnancy (the Fetal Outcome Retrospective TopiRamate ExpoSure Study [FORTRESS]).

FORTRESS is a retrospective observational study utilizing existing electronic healthcare databases (HealthCore, OptumInsight, Kaiser Southern California, and Thomson Reuters) to estimate the prevalence ratios of OCs and MCMs in the offspring of women exposed to topiramate during the first trimester of pregnancy when compared with women without first trimester topiramate exposure. FORTRESS is expected to include approximately 2,000 mother-infant dyads and is believed to be the largest retrospective topiramate medical claims study ever completed. Three cohorts are being assessed: the topiramate cohort comprised of women exposed to topiramate during the first trimester of pregnancy; the FE cohort comprised of women formerly exposed to topiramate or any other AED but not during the

first trimester of pregnancy; and the SMP cohort comprised of women with a similar medical profile to the topiramate cohort by topiramate indication (e.g., epilepsy, seizure, migraine, other) independent of AED exposure. The co-primary endpoints are the relative risk of MCM and OC. The study will be completed in the second half of 2012.

Interim FORTRESS results of over 1,500 mother-infant dyads pooled across the four study populations have been evaluated. The interim results are based on outcomes identified by electronic data (i.e., health insurance claims or electronic medical records) but not yet validated by medical record review. Moreover, the SMP cohort results, presented below, are based on anomalously low prevalence of outcomes in the HealthCore database which, when investigated, were found to result from a statistical aberration capturing only 1 case of OC on initial sampling, while on repeated sampling the mean was 5 cases of OC. The comparison with the FE cohort therefore likely provides the most reliable estimate of the FORTRESS data collected to date.

With these caveats, the interim FORTRESS data indicate that the OC prevalence ratio for the TPM versus FE cohorts standardized by center-specific propensity score decile was 2.45 (95% CI, 0.97−6.18). The similarly standardized OC prevalence ratio for the TPM versus SMP cohort was 6.46 (95% CI, 2.07−20.17). The most valid comparison for assessing the effect of TPM is one that excludes women on AED polytherapy (i.e., women taking both TPM and other AEDs in the first trimester). The OC prevalence ratio for the TPM monotherapy cohort versus FE cohort standardized by center-specific propensity score decile was 2.00 (95% CI, 0.71−5.68). The similarly standardized OC prevalence ratio for the topiramate monotherapy cohort versus the SMP cohort was 5.71 (95% CI, 1.75−18.58). Because of the anomalously low prevalence of OC in the SMP cohort, a follow-up analysis of this control cohort is underway to better examine the prevalence ratio of TPM monotherapy cohort versus the SMP cohort.

Analyses of data on all major congenital malformations is in process, and will be made available once final validated results have been obtained.

6.3.5 AERS Database and Exposures

The AERS database is a collection of spontaneously reported events with no control comparators such that valid conclusions regarding causal relationships cannot be drawn. In addition, due to the spontaneous nature of the reported data, there is a reporting bias and AERS data cannot be used to calculate the true incidence of an adverse event in the United States (FDA Guidance 2002). Nonetheless, VIVUS conducted an assessment of teratogenicity reports for topiramate in the AERS database.

Topiramate has been on the market at substantially higher doses than those in QNEXA for over 15 years. In the last 5 years, approximately 27 million prescriptions were filled for WOCBP in the U.S. (IMS data). The AERS database contained 67 spontaneous reports of all malformations (major and minor) associated with administration of topiramate monotherapy in pregnancy (FDA Comunication at EMDAC, July 2010). The malformations were equally distributed between craniofacial, skeletal, and cardiovascular malformations. The pattern was

consistent with common congenital malformations seen in the general population (Yoon 2001).

6.4 QNEXA Clinical Trial Experience

Table 56 summarizes the number of pregnancies that occurred during the QNEXA clinical development program. Overall, 34 pregnancies were reported: 29 in subjects on active treatment and 5 in subjects on placebo. All 19 births were associated with healthy normal newborns and 6 pregnancies resulted in spontaneous miscarriages. None of these pregnancies has been associated with adverse outcomes, except a single ectopic pregnancy that was reported as an SAE.

The pregnancies that subjects elected to carry to term were commonly considered high risk, complicated by the subjects' age, obesity and obesity-related comorbidities, and/or pre-existing medical or obstetrical conditions. All infants were delivered at term, and documentation of newborn examinations was received in all cases. The average gestational age at diagnosis was 38 days (5.4 weeks), a period that is the most sensitive for malformations. There were no congenital anomalies seen on physical examination and routine newborn assessments in any infant.

Table 56. Pregnancy Outcomes by Treatment Group – Studies OB-118, OB-205, OB-301, OB-302, OB-303 and OB-305

Outcomes, n	Placebo	QNEXA[a]	PHEN 15 mg	TPM 46 mg	TPM 92 mg	QNEXA Low	QNEXA Mid	QNEXA Top	TOTAL[b]
Pregnancies	5	3	2	1	2	1	3	17	**34**
Births with congenital abnormality	0	0	0	0	0	0	0	0	**0**
Healthy live births	3	1	1	1	1	1	2	9	**19**
Spontaneous abortions	1	1	0	0	0	0	0	4	**6**
Elective abortions	1	0	1	0	0	0	0	4	**6**
Ectopic pregnancies	0	1	0	0	0	0	0	0	**1**
Unconfirmed pregnancy	0	0	0	0	1	0	0	0	**1**
Lost to follow-up	0	0	0	0	0	0	1	0	**1**

a. Unable to determine dose due to study design.
b. As of June 3, 2010.
PHEN = phentermine; QNEXA = fixed-dose combination of phentermine and topiramate; TPM = topiramate.
QNEXA Low, 3.75 mg/23 mg; QNEXA Mid, 7.5 mg/46 mg; QNEXA Top, 15 mg/92 mg.

6.5 Discussion

The conclusions from recent data on OC support the continued labeling of topiramate-containing products with information regarding potential risk. Since the initial QNEXA NDA submission, the prevalence of MCMs with topiramate exposure has been examined in three separate studies. A recent population study of all births in Denmark (837,795 infants) over a 12-year period revealed that the adjusted prevalence odds ratio for MCM following first trimester exposure to topiramate (versus no AED exposure) was 1.44 (95% CI, 0.58–3.58) (Molgaard-Nielsen 2011). In the case-control study from the BDS and NBDPS surveillance programs, a total of 33,825 MCMs were evaluated; and the adjusted odds-ratio for topiramate

(versus no AED) exposure was 1.01 (95% CI, 0.37–3.22) (Margulis 2011). Lastly, in the retrospective cohort study from the Wolters Kluwer Pharma Solutions Source® Lx Patient Longitudinal claims database, relative risk values for patients exposed to topiramate during the first trimester of pregnancy compared to various control groups designed to match patients by diagnosis ranged from 0.87 (0.59–1.29) for the comparison with patients with a diagnosis of epilepsy, to 1.32 (0.88–1.97) for the comparison with patients exposed to other AEDs. This study also indicated that the MCM prevalence following first trimester topiramate exposure may be lower than the prevalence in patients with a diagnosis of diabetes (RR 0.61; 95% CI, 0.43–0.87).

The retrospective cohort study using Wolters Kluwer claims data demonstrated prevalence rates for OC of 0.23% following first trimester topiramate exposure, compared to prevalences that ranged from 0.16% to 0.31% across the various comparator cohorts. In general, these prevalence rates are fairly close to the expected background prevalence of approximately 0.15%, and far under the prevalence initially identified in the NAAPR study (1.4%). While the prevalence in the TPM cohort was not significantly higher than the prevalence in any of the comparator cohorts, observed upper bounds for the 95% confidence intervals of relative risks between cohorts ranged from 3.7 to 6.9. Despite identifying 870 mother/infant dyads with topiramate exposure during the first trimester of pregnancy, the number of clefts observed in this study may be insufficient to rule out relative risk values less than 4. While this study did not show significant differences between cohorts, it also did not provide sufficient assurance that no signal was present.

Studies conducted to date indicate that topiramate exposure during the first trimester of pregnancy at doses higher than those proposed in QNEXA has no effect on the prevalence of MCMs overall, but may result in an increase of approximately 2-fold (based on cohort studies) or up to 5-fold (based on case-control studies) in the prevalence of oral clefts, and support existing topiramate prescribing information.

7 PROPOSED RISK MITIGATION FOR QNEXA

Because of the potential teratogenicity risk of topiramate based on present data, and the use of QNEXA, which contains low doses of topiramate, for a new therapeutic indication (obesity), VIVUS is committed to implementing risk mitigation activities designed to minimize the risk of fetal exposure to QNEXA that exceed the current risk mitigation activities that are employed for topiramate for the management of migraine and epilepsy. VIVUS have been working collaboratively with FDA on developing a risk mitigation program, including a REMS, for QNEXA. The program is currently still under discussion with the FDA, however, the following plan provides context for a proposed set of activities that VIVUS believes is appropriate for QNEXA.

FDA has advised VIVUS that the QNEXA risk management program, and specifically the REMS, should not be designed to restrict access to QNEXA or create a burden to healthcare delivery. FDA further advised that VIVUS should consider whether any significant inconsistencies between the proposed QNEXA risk mitigation program and the existing labeling for topiramate could result in patients with obesity being inappropriately prescribed

single-agent topiramate products that are not distributed with the agreed-upon QNEXA educational elements. For context, topiramate does not currently have a REMS, but does include a Medication Guide with the package labeling.

With this guidance, the QNEXA risk mitigation program will consist of the FDA-approved full prescribing information (also known as the PI, package insert, or label), a Risk Evaluation and Mitigation Strategy (REMS) comprised of Medication Guide, Communication Plan, Elements to Assure Safe Use (ETASU) and Assessments. These efforts will be supported by additional non-REMS informational tools and measures. The objective of this section is to describe a full range of QNEXA risk mitigation activities being considered by VIVUS and FDA. As with labeling, the ultimate elements of risk mitigation programs are determined during the final stages of the FDA's review process.

Labeling plays an important part in the overall risk mitigation program. In accordance with a Pregnancy Category X designation, VIVUS expects to include a Contraindication in women who are pregnant. VIVUS had initially proposed contraindicating QNEXA in all women of childbearing potential (WOCBP), but FDA advised that this broad Contraindication was not warranted since many WOCBP could derive a benefit from QNEXA which might outweigh risk with appropriate usage. The exact language of the final Contraindications, Warnings & Precautions, and Special Populations sections of the label may contain additional information about women trying to become pregnant or those at high risk for pregnancy. Prescribers are generally familiar with Pregnancy categories, and have an understanding and significant sensitivity to products which have a Category X designation.

Regarding the REMS, VIVUS and FDA have agreed that the goals of the QNEXA REMS should be to inform and educate prescribers, pharmacists, and patients about:

- The potential serious risks of congenital malformations associated with fetal exposure to QNEXA during pregnancy, and the importance of pregnancy prevention to minimize fetal exposure; and

- The safe-use conditions for QNEXA

7.1 Medication Guide

VIVUS and FDA both agree that, in accordance with 21 C.F.R. § 208.24, a Medication Guide will be systematically dispensed with each prescription and each refill for QNEXA. The goal of a Medication Guide is to serve as a patient-focused educational tool with information about risks, how to appropriately use QNEXA and what to expect while on therapy. It will include information about the potential risks of clefts in fetuses exposed to QNEXA *in utero*, and will emphasize the importance of adequate and consistent contraceptive usage to avoid pregnancy, as well as the need to test for pregnancy, and to stop QNEXA immediately if a patient finds out that she is pregnant. The Medication Guide will make patients aware of the need to report any pregnancies to their providers and of a QNEXA pregnancy data collection program which will be established.

As discussed below, QNEXA will only be dispensed by QNEXA-certified pharmacies. Each bottle of QNEXA will include a prominent notice to alert pharmacists to "Dispense with Medication Guide." All certified pharmacies will be contractually obligated to provide a copy of the Medication Guide with each new and refill prescription. These pharmacy systems will be automated to include a copy of the Medication Guide in every shipment to patients. In addition, copies will be made available through the product website (www.QNEXA.com), a toll-free VIVUS Medical Information line, and the field-based personnel. Certified pharmacies will be notified and provided updates of the Medication Guide whenever there are revisions.

A Patient Brochure, as an adjunct to the Medication Guide, may also be included with each prescription. The benefit of a Patient Brochure is that it would serve as a colorful, patient-friendly document which could include pictures and graphics to reinforce key risk messages in the Medication Guide. Both the Medication Guide and the Patient Brochure would be pre-tested for patient comprehension. FDA has encouraged VIVUS to consider whether having two patient documents would serve to reinforce the information contained in them or potentially deter patients from reading the Medication Guide.

7.2 Communication Plan

As a second agreed upon REMS measure, VIVUS will implement a Communication Plan to U.S. healthcare providers to support implementation of the REMS. This will consist of Dear Healthcare Provider and Dear Pharmacists Letters. The Dear Healthcare Provider Letter will target obesity specialists, primary care physicians, nurse practitioners, allied health providers, endocrinologists, bariatric surgeons, and any prescribers who have written prescriptions for a weight-loss medical treatment or topiramate (for any indication) in the past 12 months. The Dear Pharmacist Letter will be provided to all U.S. certified and non-certified pharmacies.

The materials provided with these letters will include the full prescribing information and the Medication Guide. These materials, and the letters, will present information focused on the risks of teratogenicity and cleft, as well as the importance of contraceptive use and pregnancy testing recommendations for WOCBP. The materials will also highlight the implementation of a REMS for QNEXA, and explain the Prescriber Training and Pharmacy Certification Elements to Assure Safe USE. Additionally, the Communication Plan will ensure that prescribers are aware of the data collection system for any pregnancies which occur while on QNEXA, including collection of data on pregnancy outcomes.

The letters to Healthcare Providers and Pharmacists will be distributed prior to the availability of QNEXA. Additionally, the letters and materials will be available through the product website (www.QNEXA.com), a toll-free VIVUS Medical Information line, and field-based personnel.

VIVUS also intends to send the Dear Healthcare Provider letter with Medication Guide and Full Prescribing information to the leadership of medical and professional societies whose members provide care for obese patients to make them aware of the QNEXA REMS requirements, including ETASU on prescriber training and pharmacy certification, and

request that they support the REMS implementation by disseminating the information to their membership.

FDA has encouraged VIVUS to consider the appropriate frequency of recurring messages targeted to healthcare providers to balance the benefits of repetitive messaging against the potential for information fatigue.

7.3 Elements to Assure Safe Use (ETASU)

VIVUS intends to implement the following ETASU to mitigate the potential serious risks of QNEXA. These elements include a certified pharmacy distribution network, provider training, and an implementation system. Each element is described in more detail below.

7.3.1 Certified Pharmacy Distribution Network ETASU

QNEXA will be dispensed only by pharmacies that have been specifically certified and included in the certified QNEXA pharmacy distribution network. This network will consist of large, nationally-known pharmacies that home deliver nationwide. VIVUS will distribute QNEXA only to pharmacies within the certified network. In order to obtain certification, a pharmacy would need to contractually agree to comply with the QNEXA REMS as finally agreed upon with the FDA and follow the procedures and conditions described below.

- QNEXA will only be dispensed under the following conditions:
    - Each prescription is for no more than a 30-day supply with five (5) refills or less, as dictated by DEA dispensing requirements for Schedule 4 substances.
    - A copy of the Medication Guide will be distributed to each patient with each prescription and refill.
- All pharmacists and staff involved with the dispensing of QNEXA are educated and trained on the dispensing procedures.
- The pharmacy will maintain a comprehensive patient database of all prescriptions dispensed for QNEXA including patient ID, date of birth, sex, dosage strength, physician DEA number, and fill dates.
- The certified pharmacies will provide inventory tracking data to assure that QNEXA is only distributed through appropriate channels within the REMS.
- The pharmacy will permit VIVUS to conduct periodic audits to ensure that QNEXA is dispensed according to the REMS requirements.
- If the pharmacy does not comply with these requirements, its right to dispense QNEXA may be terminated.
- Pharmacies cannot redistribute or transfer QNEXA to other pharmacies or distributors outside of the network.

This network utilizes existing pharmacy systems, with automated features, that can assure provision of a Medication Guide with every prescription and every refill, as well as to collect data on patients and providers for future safety communications or program assessments. It also controls access to prevent distribution on the internet or through inappropriate dispensing venues outside the QNEXA REMS program.

7.3.2 Healthcare Provider Training ETASU

The second ETASU element is healthcare provider training in the QNEXA REMS. VIVUS will provide prescriber education and training through a number of channels, including online training programs, live and enduring REMS-focused CME activities, written materials, and information available on www.QNEXA.com.

FDA has advised VIVUS that, because healthcare providers are free to prescribe single-agent topiramate without any restrictions, that the QNEXA healthcare training ETASU should focus on reaching prescribers with training but should not be a pre-requisite for prescribing nor should it contain any restrictive element that would block prescribing access for physicians who fail to comply. Instead, current and potential QNEXA prescribers will be strongly encouraged and incentivized where possible (e.g. CME credits), to participate in QNEXA educational and training activities.

A database of healthcare providers who have been trained will be maintained and cross-referenced to the prescriber databases kept by the pharmacies to track the extent of training, prescriber knowledge and behavior, and assess changes as a result of training. These assessments will be used to understand whether additional modifications in training scope or content would be required to further improve safe use of QNEXA. VIVUS will be able to identify non-trained prescribers and target them to offer training materials and activities.

All training activities will include key learning objectives which are still under discussion with FDA. Such objectives would likely include:

- Review and understand the QNEXA Full Prescribing Information and Medication Guide;
- Understand and be able to counsel women of childbearing potential on the potential serious risks of congenital malformations associated with fetal exposure to QNEXA during pregnancy;
- Appreciate the importance of pregnancy prevention through adequate contraception and pregnancy testing to minimize fetal exposure, and the need to discontinue QNEXA immediately if pregnant;
- Recognize that QNEXA has a Pregnancy Category X designation and is contraindicated in women who are pregnant, or trying to become pregnant, and includes warnings to those WOCBP who are at high risk for becoming pregnant due to lack of adequate contraception;

- Be aware that there is a pregnancy data collection system to collect information about any pregnancies that occur while on QNEXA, including pregnancy outcomes; and that prescribers should report any pregnancies they become aware of, and encourage patients to do the same;

Understand that QNEXA can only be dispensed from a contracted and certified pharmacy.

7.3.3 Implementation System ETASU

The final ETASU component is an implementation system which will allow the structure to be put into place to accomplish the risk mitigation activities. It is planned to include the following components:

- VIVUS will collect data on all QNEXA prescribers and patients through the certified pharmacy network which will allow for broader and directed distribution of future safe use communications and identification of prescribers and patients for participation in REMS assessments.

- VIVUS will conduct data audits to monitor the certified pharmacies and ensure that QNEXA is dispensed according to the specified REMS requirements. If a certified pharmacy is found to be non-compliant, VIVUS will institute corrective action and may remove the pharmacy from the network.

- VIVUS will monitor prescriber participation in training, and continue to seek ways to expand the reach and participation in training programs.

Various data collection and analysis efforts, as well as specific REMS assessments, will be designed to continue to increase awareness of the QNEXA REMS, safe use conditions and improve program implementation if necessary.

7.4 REMS Assessments and Timetable

VIVUS will submit REMS assessments to FDA at 6 and 12 months, and then annually thereafter, from the date of the approval of the REMS.

7.5 Additional Risk Mitigation Considerations

Based on publicly available information about experience with other approved products that require or recommend contraceptive use and pregnancy testing, both the FDA and VIVUS acknowledge that additional creative efforts are needed to better ensure that patient contraception use is consistent to avoid unintended pregnancies and that pregnancy testing occurs routinely to allow early discontinuation of drug if pregnancy occurs. VIVUS is considering measures to increase the awareness, knowledge, and behaviors concerning adequate contraceptive counseling and use and compliance with pregnancy testing recommendations. VIVUS and FDA have been involved in ongoing discussions regarding the benefits of these tools and whether any of these additional tools should be included as risk mitigation measures.

A Patient-Provider Agreement (PPA) is a counseling tool which serves as a reminder to healthcare providers to communicate important risks, such as teratogenicity and the risk of clefts, to patients. A PPA also provides the prescriber an opportunity to seek commitment on patient compliance with contraception, use of pregnancy testing, and agreement to stop QNEXA if she becomes pregnant to assure fetal exposure *in utero* is minimized.

For providers who may not counsel on contraceptive practices as part of their ordinary practice, a Contraceptive Counseling Brochure could increase understanding and awareness, and may strengthen teaching skills on these important points. It could also potentially include patient-focused contraceptive teaching tools as well.

The FDA has advised VIVUS that mandatory in-office pregnancy testing would be overly burdensome for providers and patients and has asked that such testing not be included in the QNEXA REMS program. VIVUS has proposed voluntary monthly pregnancy testing be part of the QNEXA risk management plan to identify unintended pregnancy early, to stop QNEXA, and thereby minimize duration of fetal exposure *in utero*. Information about the need for pregnancy testing would be included in all of the healthcare provider and patient educational materials, including the Patient-Provider Agreement. Specific ways to implement and increase compliance with effective pregnancy testing in appropriate patients without undue burden are still under discussion with FDA.

Data regarding pregnancies occurring on QNEXA, including reasons for pregnancy (and information on contraceptive practices), and pregnancy outcomes will be collected by VIVUS. Information about the existence of such a data collection system will be included in the label, Medication Guide, all HCP and patient communications as well as through www.QNEXA.com, a toll-free VIVUS Medical Information line and field-based VIVUS personnel. The initial intake step in this system would also include a reminder to patients to stop taking QNEXA, and would reinforce existing messages on this subject. The data collection may occur under a pregnancy registry or a pregnancy-focused enhanced pharmacovigilance system still to be discussed with FDA. Data would be collected to allow for root cause analysis of pregnancies to inform modifications or improvements to future risk mitigation activities.

Additional voluntary tools to assist patients and providers in the safe use of QNEXA may include Patient Selection Checklists and Algorithms to Guide Initiation and Ongoing Maintenance of Therapy, including guidance around stopping rules from the label. The planned online Patient Support Program is designed to support behavioral, nutrition, and physical activity changes while on QNEXA, and will include prominent safety messaging, including outbound reminders for patients who sign up and provide their contact information when enrolling in the QNEXA Patient Support Program.

Both VIVUS and FDA agree that a risk management program, including a robust REMS, will be implemented and VIVUS is fully committed to support these safe use activities. FDA and VIVUS continue to engage in detailed, collaborative discussions regarding the QNEXA risk management plan and appreciate EMDAC's advice on the appropriate balance of risk mitigation elements for QNEXA.

8 POST-MARKETING COMMITTMENTS

VIVUS is currently exploring the feasibility of conducting an active surveillance safety study through a health maintenance organization to monitor for the occurrence of pregnancies and pregnancy outcomes in WOCBP as well as major adverse cardiovascular events (MACE) in men and women using QNEXA in the post-approval setting. The study will compare the occurrence of these outcomes to a control cohort matched for certain baseline characteristics (ex. age, BMI, and gender) not treated with QNEXA. The goal of this surveillance study is to provide periodic assessment of these outcomes of interest for enhanced pharmacovigilance. If feasible, VIVUS plans to implement such a study at the time of launch of QNEXA with results available 12 months thereafter.

VIVUS plans to conduct a post-approval superiority cardiovascular outcome trial (CVOT) to evaluate the effect of long-term treatment with QNEXA on the incidence of nonfatal MI, nonfatal stroke, or cardiovascular death and other relevant efficacy and safety endpoints in obese subjects with cardiovascular disease or cardiovascular disease risk factors **(Appendix 4).**

9 BENEFITS AND RISKS

The clinical program for QNEXA was conducted in accordance with the FDA's Obesity Guidance. On the basis of accumulated evidence of the long-term health consequences of obesity and its comorbidities, the FDA has supported the development of safe pharmacologic therapies to be used long term for weight management in individuals at particular risk. Individuals with BMI ≥30 or ≥27 kg/m^2 who also have weight-related comorbidities are considered appropriate candidates for receiving treatment with weight-management drugs and were included across the QNEXA development program.

The Phase 3 studies of QNEXA included three dose levels: QNEXA Low dose, QNEXA Mid dose, and QNEXA Top dose. QNEXA Mid dose is the recommended treatment dose. QNEXA Top dose is intended for subjects on QNEXA Mid dose who have not achieved adequate weight loss or improvements in weight-related comorbidities. QNEXA Low dose is the recommended starting dose and may be considered for chronic use as a treatment dose in some subjects based on their individual treatment goals and/or their ability to tolerate the Mid dose. The doses of phentermine (15 mg) and topiramate (92 mg) that comprise QNEXA Top dose are substantially lower than the maximum approved doses of either monotherapy for its respective indications.

The design and analyses of the QNEXA clinical program focused on subjects at high risk for obesity-related morbidity and mortality, thus representing a population with high medical need. The largest pivotal studies, study OB-302 and study OB-303, were specifically designed to assess the effect of QNEXA treatment on subjects who are morbidly obese and subjects with weight-related comorbidities, respectively.

The effects of QNEXA on weight loss were substantial and exceeded the FDA efficacy benchmarks for clinically significant weight loss. Additionally, significant drug-related improvements in comorbidities were observed with QNEXA treatment.

There was no evidence of any new or unexpected safety issue with QNEXA relative to phentermine or topiramate monotherapy. Based on thorough evaluations of clinical status, laboratory assessments, review and analysis of adverse events, use of questionnaire instruments to assess cognitive function as well as mood and suicidality, and study of potential psychomotor effects of QNEXA, there were no signals of unexpected significant adverse effects in any of these areas during the clinical program.

9.1 Benefits of Treatment

9.1.1 Treatment Effects on Weight-Related Parameters

Placebo-subtracted weight-loss results across each of the Phase 3 studies were not only statistically significant but also compared favorably to the labeled effects of currently approved weight-loss therapies. Low dose QNEXA is associated with a placebo-subtracted weight loss of approximately 3.5% after 1 year of treatment. Higher doses of QNEXA resulted in placebo-subtracted weight loss of up to 9.4% after 1 year of treatment. Patients who tolerated and used QNEXA for the intended treatment course lost nearly 14% of their baseline body weight.

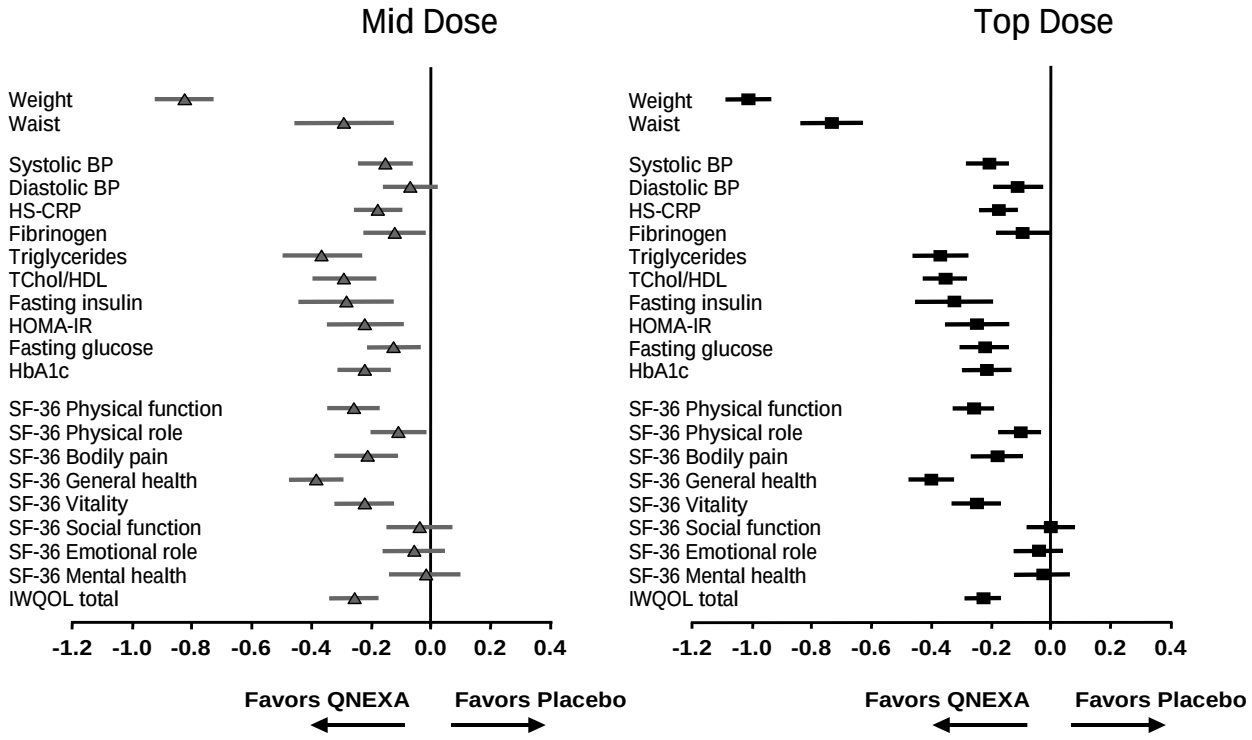
With respect to the categorical assessment of weight loss, significantly greater proportions of subjects treated with QNEXA Low, Mid, and Top dose achieved at least 5%, 10%, and 15% weight loss compared with placebo. From the ITT analysis with LOCF, the response rates for at least 5% weight loss from baseline in study OB-302 and study OB-303 were 67% and 70%, respectively, with QNEXA Top dose treatment, and 17% and 21%, respectively, with placebo treatment. At least 10% weight loss was achieved by approximately two-thirds of subjects who completed 56 weeks of treatment with QNEXA Top dose (68% in study OB-302 and 64% in study OB-303). At least 15% weight loss was also achieved by a substantial proportion of subjects who completed 56 weeks of treatment with QNEXA Top dose (48% in study OB-302 and 39% in study OB-303). Integrated analyses demonstrated that the response rates for 5%, 10%, and 15% weight loss from baseline were statistically significant and consistent with the results of the individual studies. Extension of study OB-303 for an additional year in study OB-305 demonstrated maintenance of QNEXA weight loss efficacy when compared to placebo.

The integrated 1-Year Cohort analyses also demonstrated that treatment with QNEXA resulted in clinically and statistically significant weight loss in all subgroups examined, defined by sex, age, race, and baseline BMI. Study-specific and PK/PD analyses indicate that the effect of QNEXA Top dose treatment on weight loss is generally greater with increasing baseline BMI and suggest that weight loss continues for a longer period of time with increasing BMI. In study OB-302, weight loss was progressive through Week 56 in the QNEXA Top dose group, which included subjects with a higher mean baseline BMI (42.1 kg/m^2) than study OB-303 (36.6 kg/m^2). In study OB-303, weight loss in the QNEXA Top dose group remained stable beyond Week 40. In study OB-305, weight loss with

QNEXA remained stable until Week 72 with QNEXA Top dose and Week 84 with QNEXA Mid dose. For the placebo group, a slight upward trend from the treatment nadir at Week 28 continued to end of study.

As shown in **Figure 31**, a number of secondary and exploratory efficacy parameters were assessed to investigate whether the weight loss associated with QNEXA therapy was accompanied by the expected overall beneficial effects on obesity-related metabolic abnormalities and cardiovascular risk factors. These parameters included waist circumference, blood pressure, lipids, glucose metabolism and quality of life measures.

Figure 31. Summary of QNEXA Benefits (Placebo-Subtracted Effect Size, 95% Confidence Interval)



BP = blood pressure; HbA_{1c} = hemoglobin A1c; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; HS-CRP = high-sensitivity C-reactive protein; IWQOL = Impact of Weight on Quality of Life; QNEXA = fixed-dose combination of phentermine and topiramate; SF-36 = Short-Form 36; TChol = total cholesterol;

9.1.2 Treatment Effects on Waist Circumference

Increased visceral or abdominal adiposity, independent of BMI, is associated with increased cardiovascular and mortality risk through a variety of mechanisms (Pischon 2008; Janssen 2004; Zhu 2002; Rexrode 1998). Waist circumference is a simple, convenient measure and serves as a surrogate for visceral abdominal adipose tissue, as it correlates with computerized tomography- or magnetic resonance imaging-derived measurements of visceral fat content (Pi-Sunyer 2004). Accordingly, reductions in waist circumference, reflecting reductions in visceral adiposity, may be associated with an improved cardiovascular risk

profile. Mean reductions in waist circumference of up to 13.9 cm were significantly greater with QNEXA treatment than with placebo.

9.1.3 Treatment Effects on Weight-Related Comorbidities

Drug-related improvements in weight related comorbidities were of the greatest magnitude in study OB-303, which by design included overweight and obese subjects who had two or more comorbidities at baseline. The effects of QNEXA on the relevant disease markers and risk factors observed in the pre-specified OB-303 comorbidity subpopulations were numerically larger compared with the overall study population or the integrated cohorts. Moreover, the baseline upper quartile analyses, which included subjects with the highest degree of comorbidities, demonstrated the greatest absolute drug effects. Taken together, the analyses of data from the different populations (study-specific and integrated ITT sets, comorbidity subpopulations, and upper quartiles) support the conclusion that QNEXA is effective in promoting weight loss and health improvements across the spectrum of obesity and comorbidity severity, and it is associated with more pronounced effects in subjects with more significant disease at baseline.

Treatment with QNEXA resulted in significant improvements in SBP and DBP relative to placebo. In the integrated analysis cohorts, treatment with both QNEXA Top and Mid dose resulted in significant improvements in SBP relative to placebo at Week 56. QNEXA Top dose treatment resulted in significant improvements in DBP relative to placebo at Week 56. The overall effects on SBP and DBP were greatest in study OB-303, where the overall reductions in blood pressure were driven by the effects in approximately 50% of randomized subjects with hypertension at baseline. The largest mean reductions in blood pressure were observed in the subpopulation of subjects with hypertension and in subjects with baseline SBP and DBP in the upper quartiles of the study population. In addition, compared with placebo subjects, a higher proportion of QNEXA-treated subjects had reductions in the number of concomitant antihypertensive medications and a lower proportion had increases in concomitant antihypertensive medications.

Treatment with QNEXA also resulted in significant improvements in lipid parameters relative to placebo. In the integrated analysis cohorts, treatment with QNEXA Top and Mid dose resulted in significant improvements in TC and TG relative to placebo at Week 56. Treatment with QNEXA Top and Mid dose resulted in significant improvements in HDL-C relative to placebo at Week 56. QNEXA Top dose treatment resulted in significant improvements in LDL-C relative to placebo at Week 56. Additionally, treatment with QNEXA Top and Mid dose resulted in clinically meaningful reductions in TG and increases in HDL-C, without increasing LDL-C in the subpopulation of subjects with hypertriglyceridemia at baseline in study OB-303. Consistent with other study-specific comorbidity subpopulation results, subjects in study OB-303 with hypertriglyceridemia and baseline lipid values in the upper quartiles (or lower quartile for HDL-C) demonstrated the largest numerical changes in lipid parameters.

Effects on glycemic endpoints were observed in an overall population as demonstrated by the results of the integrated analyses; however, the most pronounced glycemic effects with QNEXA treatment were observed in diabetic and insulin-resistant pre-diabetic subjects.

Treatment with QNEXA Top and Mid dose significantly reduced HbA_{1c} and fasting serum glucose relative to placebo at Week 56.

The effects of QNEXA treatment on HbA_{1c} and fasting serum glucose were greater in subjects with diabetes in studies OB-303 and DM-230 than in the 1-Year Cohort. The changes in HbA_{1c} and fasting serum glucose observed in the subpopulation of subjects with diabetes in study OB-303 were consistent with the results from the Phase 2 studies conducted in subjects with diabetes (study OB-202 and extensions DM-230 and DM-231). Notably, the mean baseline HbA_{1c} among the approximately 350 subjects with type 2 diabetes in study OB-303 was 6.8%, marking relatively good average glycemic control. In study OB-202, which enrolled obese subjects with type 2 diabetes, the mean baseline HbA_{1c} was 8.7%, and larger reductions in HbA_{1c} were observed at study endpoint for this population than for subjects with diabetes in study OB-303.

Development of type 2 diabetes is generally preceded by an established pattern of hyperinsulinemia and increased insulin resistance. In the at-risk population treated in study OB-303, QNEXA treatment resulted in clinically and statistically significant decreases in fasting insulin levels and insulin resistance as assessed by HOMA-IR, compared with placebo. As a result, among nondiabetic subjects treated in this study program, there was a statistically significant 58% reduction in the annualized incidence of newly diagnosed type 2 diabetes in subjects treated with QNEXA compared to placebo in the 1-Year Cohort (OB-303). Additionally, there was a statistically significant 76% reduction among patients in the 2-Year Cohort (OB-305). Taken together, the clinical trial data strongly support a benefit of QNEXA-associated weight loss on glycemic control in subjects with type 2 diabetes, and on delaying the onset of type 2 diabetes in normoglycemic and prediabetic subjects.

9.1.4 Treatment Effects on Biomarkers of Cardiovascular Disease Risk

Effects of treatment on biomarkers of cardiovascular disease risk, such as hs-CRP, adiponectin, and fibrinogen, were measured in study OB-303. Treatment with QNEXA Top and Mid dose resulted in statistically significant mean changes in hs-CRP, adiponectin, and fibrinogen. The magnitude of reduction in hs-CRP appears to be comparable to those observed in the JUPITER trial with rosuvastatin (Ridker 2008).

9.2 Risks of Treatment

The safety and tolerability profile of QNEXA demonstrated in the clinical development program is consistent with the known adverse effects of the approved component agents when used as monotherapy for various indications. Adverse effects observed with phentermine and topiramate monotherapy, which inform current labeling, were generally observed in subjects treated with doses higher than those studied in the QNEXA clinical development program.

Phentermine, a sympathomimetic amine, acts centrally through norepinephrine release. Central nervous system adverse events associated with its use include overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, and headache. Cardiovascular system events, including palpitations, tachycardia, and elevation of blood pressure, and

gastrointestinal events, including dry mouth, unpleasant taste, diarrhea, and constipation, are also described.

Topiramate, is most commonly associated with adverse events related to the central nervous system. These adverse events include somnolence, fatigue, confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, mood disorders, and paresthesia related to its pharmacology as a carbonic anhydrase inhibitor. Topiramate also carries a label warning for teratogenicity.

From the integrated safety analyses of the QNEXA clinical program, the commonly observed adverse events associated with QNEXA treatment are known side effects of one or the other component agent and do not represent novel side effects engendered through the combined pharmacology of the two drugs. Furthermore, some of the expected side effects of topiramate, such as paresthesia, somnolence, psychomotor slowing, and difficulty with memory, occurred at a lower incidence with QNEXA treatment than cited in the product label for topiramate monotherapy. The lower incidence of these events may be due to the lower doses of topiramate in the fixed-dose combinations, the modified-release formulation of topiramate, or the oppositional pharmacodynamic effects of the phentermine component.

The safety results for the integrated 1-Year Cohort and the 2-Year Cohort indicate that long-term QNEXA treatment did not result in any new types of adverse events or substantially increased rates of adverse events. In the 1-Year Cohort, the overall incidence of TEAEs was higher in the QNEXA dose groups than in the placebo group (placebo, 76.0%; Low dose, 80.0%; Mid dose, 85.1%; Top dose, 87.2%).

The most frequently reported TEAEs with QNEXA treatment were paresthesia (17.0%), dry mouth (16.6%), constipation (15.1%), upper respiratory tract infection (13.5%), nasopharyngitis (10.0%), and headache (9.8%).

The incidence of SAEs in the 1-Year Cohort was low and similar across the treatment groups (placebo, 3.3%; Low dose, 2.5%; Mid dose, 2.8%; Top dose, 3.6%). The incidence of cardiac SAEs was not increased in QNEXA-treated subjects relative to placebo-treated subjects. The percentage of subjects who discontinued study drug due to a TEAE was higher in the QNEXA treatment groups than in the placebo group (placebo, 8.4%; Low dose, 11.3%; Mid dose, 11.6%; Top dose, 17.3%). The incidence of SAEs was also similar across the treatment groups in the 2-Year Cohort.

QNEXA treatment was associated with a higher incidence of cognitive adverse events, although most of these events were mild in severity, none was serious, and discontinuations attributable to cognitive impairment were infrequent. The QNEXA Top dose and Mid dose groups showed a higher incidence of anxiety-related adverse events, and the QNEXA Top dose group was associated with a higher incidence of depression adverse events. Mood-related adverse events were primarily mild in severity and none was serious. Study drug discontinuation for each of these TEAEs was <2%, and overall, there was no difference between the QNEXA groups and placebo with respect to the use of new antidepressant or psychiatric medications.

All treatment groups had mean decreases in the PHQ-9 total score, indicating overall improvement in the presence and severity of depression. No clinically important differences were observed among the treatment groups in mean changes in the PHQ-9 score. The summary of worsening shifts in PHQ-9 depression severity by treatment group likewise did not reveal any consistent treatment-related patterns. Therefore, with regard to PHQ-9-assessed depression, the effects of treatment with QNEXA were not distinguishable on a population basis from those of placebo.

No differences were observed among the treatment groups in responses on the C-SSRS and PHQ-9 assessments of suicidal behavior and suicidal ideation. No subject in the 1-Year and 2-Year Cohorts had a positive response to the C-SSRS composite measure at any time point after randomization. No significant differences were observed among the placebo group and the QNEXA groups regarding the incidence or emergence of suicidal behavior or suicidal ideation.

No clinically important differences were noted among the treatment groups in changes in safety laboratory parameters. In the individual studies, there were no important differences among the treatment groups in changes in physical examination findings at the final study visit. The percentage of subjects with new/abnormal findings on auscultation of the heart, such as abnormal heart sounds and murmurs, were similar with QNEXA treatment and placebo treatment. Furthermore, the results from the thorough QT/QTc study (study OB-118) demonstrated that QNEXA treatment does not cause QT prolongation; and the echocardiographic data from study OB-201 showed that QNEXA treatment does not result in changes in heart valve morphology. The overall safety evaluation indicated no signal for cardiovascular risk with QNEXA treatment.

Treatment with QNEXA is associated with small mean increases in heart rate in conjunction with substantial decreases in blood pressure resulting in no change between QNEXA- and placebo-treated subjects in the mean rate-pressure product, an indicator of cardiac oxygen demand. As a result, the cardiovascular response to QNEXA differs substantially from the cardiovascular response to other sympathomimetic drugs used for weight loss (i.e., sibutramine), which increase both heart rate and blood pressure. Consistent with the profiles of numerous other drugs associated with small heart rate increases, detailed analysis of serious adverse events in the QNEXA program by various groupings showed no signal of increased adverse outcomes in cardiovascular or neurovascular events. In addition, the temporal pattern of change in heart rate and blood pressure in 43 subjects who experienced serious cardiac or neurovascular events did not reveal an association of these SAEs to antecedent changes in heart rate or blood pressure.

Any risk from QNEXA's effect on heart rate is small and manageable in the context of demonstrated durable weight loss of greater than 10% at the end of two years. In a recent pooled analysis of 1.46 million adults who had never smoked, even modest increases in BMI above 30 kg/m^2 were associated with significant increases in 10-year all-cause and cardiovascular mortality. Using subjects with a BMI of 22.5 to 25.0 as the reference group, the Cox-proportional hazard ratio for all-cause mortality in women was 1.44 for subjects with a BMI of 30.0 to 34.9; 1.88 for those with a BMI of 35.0 to 39.9; and 2.51 for those with a BMI of 40.0 to 49.9. Similar increases in hazard ratios were observed in men. For

cardiovascular mortality, the increased risk associated with obesity was even more dramatic, with 10-year hazard ratios of 2.04 for subjects with a BMI of 30.0 to 34.9; 3.05 for those with a BMI of 35.0 to 39.9; and 4.42 for those with a BMI of 40.0 to 49.9 (Berrington de Gonzalez 2010). The mean BMI at baseline of subjects in the QNEXA 1-Year Cohort was 38. Thus, the treatment population was subject to a two-fold increase in the risk of all-cause mortality and to a three-fold increase in the risk of cardiovascular mortality. The weight-loss benefits of QNEXA (demonstrated to be associated with favorable changes in blood pressure, lipids, insulin sensitivity, markers of inflammation, and reduction in waist circumference in the QNEXA investigational program) are significant and expected to confer major health benefits to patients that VIVUS believes outweigh the small heart rate elevations seen in the Phase 3 program.

Finally, in terms of teratogenicity, although topiramate may carry an increased risk of congenital anomalies, its approved labeling allows for use in pregnant women in certain situations. No malformations have been reported with QNEXA and, other than the lower recommended dose in QNEXA, there is no reason to believe that QNEXA's teratogenic potential is different from that of topiramate alone. Recognizing that the obesity population in the U.S. is significantly larger than the seizure and migraineur populations, QNEXA is intended to be distributed with a risk mitigation program, including REMS and other voluntary measures aimed at minimizing fetal exposure to topiramate.

9.3 Benefit-Risk Conclusions

QNEXA represents a major advance in obesity treatment. The ability of QNEXA to produce durable weight loss can be expected to contribute greatly toward ameliorating some of the consequences of obesity and weight-related comorbidities. Consequently, the benefits of QNEXA-associated weight loss are expected to far outweigh the generally mild and manageable side effects of the treatment. On the basis of extensive efficacy and safety data from clinical studies, QNEXA demonstrates a favorable benefit/risk profile when used as an adjunctive measure in the management of overweight and obesity.

Treatment with QNEXA is highly effective for weight loss across a broad population of obese subjects, with a similarly broad range of obesity-related comorbidities. Both by measures of central tendency and response rates for various degrees of weight loss from baseline, QNEXA treatment was markedly effective in a high proportion of subjects in promoting durable weight reduction and in ameliorating the course of obesity-related comorbidities. The greatest weight-loss effects were observed among subjects with the highest baseline BMI, and the benefits of weight reduction with QNEXA treatment on cardiovascular, metabolic, and glycemic parameters were greatest for subjects with the most marked abnormalities at baseline.

Using the upper quartile of baseline values for various metabolic parameters, as defined by the population of subjects treated in OB-303, and the changes in these parameters in at-risk subjects after 1 year of treatment with QNEXA, the typical at-risk QNEXA patient can expect to achieve not only significant weight loss, but also clinically meaningful reductions in blood pressure, HbA_{1c}, LDL-C, and TG, and increases in HDL-C **(Table 57)**.

Table 57. Upper-Quartile Analysis of Cardiometabolic Risk Factors – Study OB-303

Parameter	Mean Baseline Upper Quartile Value	Post-Treatment Value QNEXA Top
Blood pressure	147/92 mmHg	126/81 mmHg
HbA_{1c}	7.3%	6.7% (<ADA goal)
HDL-C	33 mg/dL	21% increase
LDL-C	171 mg/dL	18% decrease
TG	268 mg/dL	37% decrease

ADA = American Diabetes Association; HbA_{1c} = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; QNEXA = fixed-dose combination of phentermine and topiramate; TG = triglycerides.
QNEXA Top, 15 mg/92mg

QNEXA treatment was safe and generally well tolerated by overweight and obese subjects with and without weight-related comorbidities. Several of the most commonly observed adverse events, notably paresthesia, dry mouth, dysgeusia, and insomnia, are well known and characterized side effects of one or the other component agent, and do not represent novel side effects engendered through the combined pharmacology of the two drugs. QNEXA treatment was associated with a higher incidence of insomnia, depression, anxiety and cognitive adverse events. However, the actual incidence rates were generally low, most of these events were mild in severity, none of these events was serious, and discontinuations were infrequent. These events generally occurred early in treatment, were manageable, and resolved without sequelae.

Current pharmacotherapies used in conjunction with diet and exercise can achieve modest weight loss in the range of 5%, while surgical interventions, which can achieve >15% weight loss, are invasive and often times result in postsurgical complications. The treatment gap between existing pharmacotherapies and surgical interventions is clear. Currently, there is no effective non-invasive treatment capable of achieving, in a broad population, a meaningful degree of weight loss of 10% with associated improvements on numerous cardiometabolic and inflammatory risk factors. QNEXA represents a significant advance in medical therapy for treatment of obesity and management of weight-related comorbidities. For obese individuals, the adverse impact of obesity on health outcomes is well documented. Based on the results of the trials conducted in support of the NDA, among the high percentage of treated subjects who respond favorably to QNEXA treatment as part of a concerted weight management regimen, durable weight loss and substantial improvements in weight-related comorbidities are expected to reduce the severity of or prevent the long-term health consequences of obesity.

Collectively, the efficacy and safety results demonstrate that QNEXA fixed combination of phentermine and topiramate demonstrates a favorable benefit/risk profile when used as an adjunctive measure in the management of obesity.

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