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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 17 June 2010

FROM: Eric Colman, MD
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TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 15 July 2010, Advisory Committee meeting for phentermine/topiramate (Qnexa)

Background

Thank you for agreeing to participate in the July 15, 2010, advisory committee meeting. This meeting is being held to discuss the efficacy and safety of a fixed-dose combination of phentermine and topiramate (PHEN/TPM) for weight loss. Phentermine monotherapy was approved for the short-term treatment (i.e., a few weeks) of obesity in 1959. Topiramate monotherapy was approved in 1996 for the treatment of seizures and in 2004 for migraine prophylaxis.

PHEN/TPM is available in three dosages: low-dose (3.75 mg PHEN/23 mg TPM), mid-dose (7.5 mg PHEN/46 mg TPM), and high-dose (15 mg PHEN/92 mg TPM). Vivus, the company developing PHEN/TPM, is seeking regulatory approval of the following indication:

PHEN/TPM is indicated for the treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise. PHEN/TPM is recommended for obese patients ($BMI > 30 \text{ kg/m}^2$) or overweight patients ($BMI > 27 \text{ kg/m}^2$) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).

In 2007 the Division issued a draft guidance entitled Developing Products for Weight Management. The guidance stipulates that a drug will be considered effective if at least one of the following criteria is satisfied after one year of treatment:

- 1 The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant
- or
- 2 The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Efficacy of PHEN/TPM

The long-term efficacy of PHEN/TPM was assessed in two randomized, double-blind, placebo-controlled 56-week trials, OB-302 and OB-303. Study OB-302 enrolled individuals with BMIs $\geq 35 \text{ kg/m}^2$ without significant weight-related co-morbidities, whereas study OB-303 enrolled individuals with lower BMIs if accompanied by weight-related co-morbidities including hypertension, type 2 diabetes, and dyslipidemia (i.e., hypertriglyceridemia). Study OB-302 randomized approximately 1300 subjects 2:1:2 to placebo, low-dose PHEN/TPM, or high-dose PHEN/TPN. Study OB-303 randomized nearly 2500 subjects 2:1:2 to placebo, mid-dose PHEN/TPM, or high-dose PHEN/TPM. Both studies included an initial 4-week titration phase. Lifestyle modification was advised for all randomized individuals using the LEARN Program for Weight Management. Individuals were provided with a LEARN manual, and site personnel were encouraged to discuss the material at individuals' regularly scheduled visits.

The majority of the study subjects were middle-aged Caucasian women. Elderly individuals (≥ 65 years) represented less than 8% of the total study population. Approximately a third of individuals had extreme obesity ($\geq 40 \text{ kg/m}^2$).

Approximately 53%, 57%, 69%, and 62% of subjects in the placebo, low-dose, mid-dose, and high-dose treatment groups, respectively, completed the 56 weeks of treatment on study drug. Adverse events were the major reason for failure to complete the studies. Nine percent of placebo subjects, 12% of low-dose and mid-dose subjects, and 18% of high-dose PHEN/TPM-treated subjects withdrew from the studies due to an adverse event.

As shown in the following table, there were statistically significant dose-related reductions in percent body weight (baseline to Week 56) in all of the PHEN/TPM-treated groups relative to placebo.

Studies	Tx group	N	Mean baseline weight (kg)	Mean weight loss (%)	LS Mean % difference vs placebo	95% CI	p-value vs placebo
Pooled OB-302 OB-303	Placebo	1477	107.5	-1.7	--	--	--
	Low-dose PHEN/TPM	234	118.6	-5.1	-3.2	(-2.1, -4.3)	<0.0001
	Mid-dose PHEN/TPM	488	102.8	-8.4	-6.7	(-6.0, -7.5)	<0.0001

Studies	Tx group	N	Mean baseline weight (kg)	Mean weight loss (%)	LS Mean % difference vs placebo	95% CI	p-value vs placebo
	High-dose PHEN/TPM	1479	107.1	-10.6	-8.9	(-8.3, -9.4)	<0.0001

In a categorical analysis, 20% of placebo-treated subjects lost $\geq 5\%$ of baseline body weight following one year of treatment versus 45%, 62%, and 69% of low-dose, mid-dose, and high-dose PHEN/TPM-treated subjects, respectively. All comparisons versus placebo were of nominal statistical significance.

PHEN/TPM-treated groups had the expected improvements in blood pressure, lipids, and glycemia.

Per the efficacy criteria outlined in the Division's 2007 draft guidance, all three doses of PHEN/TPM were efficacious for weight loss.

Safety of PHEN/TPM

Based on the individual safety profiles of phentermine and topiramate, the safety assessment of PHEN/TPM includes, but is not limited to, five areas of particular interest: teratogenicity, psychiatric-related adverse events, cognitive-related adverse events, metabolic acidosis, and cardiovascular events.

Teratogenicity

Topiramate, at doses 2-34 times the proposed maximum dose in PHEN/TPM, is teratogenic in mice, rats, and rabbits. The congenital anomalies in animals include craniofacial defects (clefts) and limb abnormalities (ectrodactyly, micromelia, and amelia). Data from antiepileptic pregnancy registries raise concern that the congenital abnormalities observed in animal studies – principally craniofacial malformations – do indeed occur with greater frequency in women treated with topiramate compared with controls.

In the PHEN/TPM development program, women of child-bearing potential were informed of the potential teratogenicity of topiramate and all agreed to use double-barrier contraception or be on stable hormonal contraception and use a single-barrier method. Moreover, women had monthly pregnancy tests during participation in the clinical trials. When a pregnancy was documented, the woman was instructed to immediately stop study drug.

There were 34 pregnancies reported during conduct of the PHEN/TPM studies. At least 17 of the pregnancies occurred in women randomized to high-dose PHEN/TPM. The estimated average gestational age at the time of pregnancy diagnosis was 5.4 weeks. Nineteen of the 34 pregnancies were carried to term. All 19 infants were reportedly born

without congenital anomaly. Thirteen of the infants were born to mothers who had been randomized to treatment with PHEN/TPM.

That 13 normal infants were born to mothers exposed to PHEN/TPM is reassuring, but this experience is much too limited to assess whether PHEN/TPM is associated with a small-to-moderate risk for fetal malformation in overweight or obese women.

As the number of pregnancies from the PHEN/TPM program demonstrates, even a rigorous, multifaceted approach to pregnancy prevention is far from 100% effective. Factors contributing to this failure no doubt include weight-loss-induced improvement in fertility and perhaps a drug-drug interaction between PHEN/TPM and oral contraceptives where the former reduces the efficacy of the latter.

If approved, the person-years of exposure to PHEN/TPM among women of child-bearing potential will be enormous.

Psychiatric-Related Adverse Events

In a recent meta-analysis of 199 placebo-controlled trials of antiepileptic drugs, including topiramate, the FDA reported that the odds ratio for suicidality was 1.8 (1.2, 2.7) for subjects treated with an antiepileptic versus placebo. Based on this information, the labels for all antiepileptics include a warning about suicidal thoughts or behavior. These suicidality data were generated from retrospective assessment of patient-reported adverse events.

The incidence of depression-related adverse events in the PHEN/TPM clinical trials was 3.4% in the placebo group, 5.0% in the low-dose PHEN/TPM group, 3.8% in the mid-dose PHEN/TPM group, and 7.7% in the high-dose PHEN/TPM group. Anxiety-related adverse events were reported with frequencies similar to those observed for depression, with nearly three times as many reports in high-dose PHEN/TPM versus placebo. Sleep-related adverse events were reported by approximately 6%, 7%, 7%, and 11% of subjects randomized to the placebo, low-dose, mid-dose, and high-dose PHEN/TPM groups, respectively.

While the overall incidence rates were low, it should be pointed out that approximately 4 to 7 times as many subjects randomized to high-dose PHEN/TPM versus placebo discontinued study participation due to anxiety-, sleep-, and depression-related adverse events.

In contrast to the aforementioned meta-analysis of antiepileptic drugs, suicidality was assessed prospectively using the Columbia Suicidality Severity Rating Scale (C-SSRS) questionnaire in all subjects at all study visits in the PHEN/TPM phase 3 clinical trials. The incidence of suicidal ideation or behavior was 0.7% in the placebo group, 0.4% in the low-dose PHEN/TPM group, 0.6% in the mid-dose PHEN/TPM group, and 0.9% in the high-dose PHEN/TPM group. There were no completed suicides in the PHEN/TPM development program.

Cognitive-Related Adverse Events

When used at doses of 100 mg to 400 mg per day for migraine prophylaxis and the treatment of seizures, topiramate is associated, in a dose-related manner, with an increased incidence of cognitive-associated adverse events including confusion, psychomotor slowing, difficulty with concentration/attention, and difficulty with memory, speech or language problems, particularly word-finding difficulties.

In the PHEN/TPM phase 3 clinical trials, subjects randomized to PHEN/TPM reported more cognitive-related adverse events compared with subjects randomized to placebo. When the attention, memory, language, and other cognitive disorders not otherwise specified subclasses were pooled, the incidence rates were 1.7%, 2.0%, 5.6%, and 7.8% in the placebo, low-dose, mid-dose, and high-dose PHEN/TPM groups, respectively. The clinical significance of these imbalances is unknown.

Metabolic Acidosis

Due to its inhibition of carbonic anhydrase, topiramate increases renal excretion of bicarbonate. As such, therapy with topiramate is associated with a normal anion gap metabolic acidosis.

In the PHEN/TPM phase 3 clinical trials, serum bicarbonate was measured at baseline and at Weeks 4, 8, 16, 28, 40, and at end of treatment. There were no per-protocol interventions for low bicarbonate values. The percentages of individuals from the placebo, low-dose, mid-dose, and high-dose PHEN/TPM groups who experienced two consecutive or an endpoint bicarbonate value below 21 mEq/L were 2.1%, 8.8%, 6.4%, and 12.8%, respectively.

Although there were no reports of severe metabolic acidosis in the PHEN/TPM phase 3 clinical trials, real-world use of PHEN/TPM in susceptible individuals (e.g., severe diarrhea, laxative abuse, chronic kidney disease) could be expected to give rise to acute metabolic acidosis with clinical sequelae including cardiac dysfunction and ventricular arrhythmias, in severe cases.

A mild, sustained metabolic acidosis increases the probability of developing nephrolithiasis and adversely affects bone structure and function. In the one-year clinical trials, there were twenty-two reported cases of nephrolithiasis in the PHEN/TPM group compared with five in the placebo group. Neither biochemical markers of bone turnover (aside from non-fractionated alkaline phosphatase) nor bone density were measured in the PHEN/TPM clinical trials.

When topiramate is used to treat seizures or prevent migraines, periodic assessment of serum bicarbonate levels is recommended.

Cardiovascular Adverse Events

Phentermine is a sympathomimetic amine. Consequently, the current labeling for phentermine contraindicates its use in subjects with advanced arteriosclerosis, cardiovascular disease, or moderate to severe hypertension. However, it must be acknowledged that this recommendation is based more on phentermine's mechanism of action than evidence from clinical trials, as there are no adequate data to assess the cardiovascular safety profile of phentermine monotherapy when used for the long-term treatment of obesity.

In the PHEN/TPM phase 3 trials, compared with placebo treatment, there were small-to-modest mean reductions in systolic and diastolic blood pressure in the PHEN/TPM groups. In contrast, treatment with PHEN/TPM was associated with small mean increases in heart rate relative to placebo. In categorical analyses, the PHEN/TPM-treated groups had greater frequencies of increases in baseline heart rate of 5, 10, 15, and 20 beats per minute compared with the placebo group. The clinical significance of the increases in heart rate is unknown.

The incidence of arrhythmia-related adverse events was 1.8%, 1.3%, 4.2%, and 4.7% in the placebo, low-dose, mid-dose, and high-dose PHEN/TPM groups, respectively. Palpitations comprised the majority of these adverse events and occurred in 12 (0.8%) placebo subjects and 27 (1.7%) high-dose PHEN/TPM subjects.

Relatively few elderly individuals or subjects with a history of myocardial infarction or stroke were enrolled into the phase 3 clinical trials. Not surprisingly, then, the overall number of ischemic cardiovascular-related adverse events in the PHEN/TPM development program was very low. Although there were no meaningful differences in the proportions of subjects per treatment group who experienced an ischemic cardiovascular-related adverse event, four "myocardial infarctions" were reported among PHEN/TPM-treated subjects versus none of the placebo subjects. In contrast, four cases of "coronary artery disease" were reported in placebo-treated subjects versus none of the PHEN/TPM-treated subjects.

Vivus is proposing to conduct a large cardiovascular outcomes trial if PHEN/TPM is approved for the treatment of obesity.

Draft Discussion Points and Regulatory Approval Question

As you read the enclosed briefing material and listen to the presentations on July 15th, please keep in mind the following discussion points and regulatory approval question, as you will be asked to respond to them at the meeting:

1. Topiramate is a teratogen in mice, rats, and rabbits at doses 2- to 34-times the proposed maximum clinical dose of PHEN/TPM. Data from antiepileptic drug pregnancy registries suggest that topiramate at doses used to treat seizures increases the risk for fetal malformations. Given the doses of topiramate in PHEN/TPM, please comment on whether you believe PHEN/TPM poses a

- teratogenic risk to the target population for weight loss. If you believe it does pose a risk, please provide your thoughts on how this should risk be managed.
2. Taking into account the results of the assessments made with the PHQ-9 and the Columbia Suicidality Severity Rating Scale, please comment on the potential significance of the increased adverse event reports of depression, anxiety, and sleep disorders in subjects treated with full-dose PHEN/TPM.
 3. Please comment on the potential significance of the increased adverse event reports of disorders of attention, memory, and language in subjects treated with PHEN/TPM.
 4. Please comment on the potential clinical significance of the decreases in serum bicarbonate observed in subjects treated with PHEN/TPM treatment.
 5. Please comment on the potential clinical significance of the increase in heart rate observed in PHEN/TPM-treated subjects.
 6. Does the overall risk-benefit assessment of PHEN/TPM (QNEXA) support its approval for the treatment of obesity in individuals with a \geq BMI 30 kg/m² or \geq 27 kg/m² with weight-related co-morbidities?

Vote: Yes/No/Abstain

If voting yes:

- Please discuss the basis for this recommendation
- Please discuss any labeling recommendations
- Please discuss whether additional studies should be conducted post-approval

If voting no:

- Please discuss basis for this recommendation
- Please discuss what additional studies would be necessary to address an outstanding deficiency/deficiencies

Clinical Briefing Document
Endocrine and Metabolic Drugs Advisory Committee Meeting
July 15, 2010

New Drug Application 22580: VI-0521 QNEXA (phentermine/topiramate)
Sponsor: VIVUS
Clinical Reviewer: Mary Dunne Roberts, MD

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Executive summary

VI-0521 or QNEXA is a fixed-dose combination of proprietary formulations of phentermine hydrochloride and topiramate developed for treatment of obesity. QNEXA, herein referred to as PHEN/TPM, has three dosage strengths, low (3.75 mg PHEN/23 mg TPM), mid (7.5 mg PHEN/46 mg TPM), and high (15 mg PHEN/92 mg TPM). Mid-dose PHEN/TPM once daily is the recommended maintenance dose.

PHEN/TPM Efficacy

The clinical development program for PHEN/TPM was designed and executed according to the guidelines outlined in the Division's 2007 draft Guidance for Developing Products for Weight Management. The pivotal efficacy data was generated in three Phase 3 studies: OB-301, -302, and -303.

A factorial study design (study OB-301) in overweight and obese healthy adults demonstrated that both mid- and high-dose PHEN/TPM achieved clinically and statistically significant weight loss compared to their respective components alone. These results translated into approximately 3% additional weight loss and roughly 20% more individuals achieving $\geq 5\%$ weight loss over a 6 month treatment period. Individuals treated with PHEN/TPM experienced higher frequencies of treatment-emergent adverse events (TEAEs) within several system organ classifications, including nervous and psychiatric, compared to their components alone. However, the TEAEs observed were not unexpected based on the known safety profiles of phentermine and topiramate.

Studies OB-302 and OB-303 were Phase 3 trials to determine the safety and efficacy of PHEN/TPM compared to placebo over a 1-year treatment period. Study OB-302 enrolled obese adults (body mass index ≥ 35 kg/m²) with limited weight-related co-morbidities and study OB-303 enrolled overweight and obese individuals with weight-related co-morbidities, including diabetes. All doses of PHEN/TPM in both studies demonstrated a statistically significant least squares (LS) mean percent weight loss as well as higher proportions of individuals achieving 5% or greater weight loss as compared to placebo thus achieving the established efficacy benchmarks set forth by the Division for weight loss. In individuals with co-morbidities (study OB-303), mid-dose PHEN/TPM demonstrated a placebo-subtracted LS mean percent weight loss of 6.6% and 62% achieved $\geq 5\%$ weight loss compared to 21% with placebo. High-dose PHEN/TPM treatment in these individuals demonstrated placebo-subtracted LS mean percent weight loss of 8.6% with 70% achieving $\geq 5\%$ weight loss from baseline after one year of treatment. Changes in weight-related co-morbidities were examined as secondary or exploratory endpoints in studies OB-302 and OB-303. In study OB-302, the placebo-subtracted waist circumference reduction was 2.5 cm and 7.8 cm with low- and high-dose PHEN/TPM treatment, respectively. Systolic blood pressure (SBP) decreased by approximately 3 to 4 mmHg over placebo with high-dose PHEN/TPM treatment in both studies. The largest LS mean percent change in LDL-C was small and occurred in individuals treated with high-dose PHEN/TPM (-8.4% and -6.9%, study OB-302 and OB-303, respectively) which was statistically significant compared to placebo. HDL-C LS mean percent increases from baseline were also small (3.5% and 6.8%) with high-dose PHEN/TPM but were statistically significant compared to placebo.

PHEN/TPM Safety

Phentermine hydrochloride was approved by the FDA in 1959 as an appetite suppressant for short-term weight loss at doses of 15, 30, and 37.5 mg and to date is the most widely-prescribed weight-loss drug. Topiramate (TOPAMAX) was approved by the FDA in 1996 for the treatment of seizures at doses up to 400 mg/day in adults and in 2004 for the prevention of migraine headaches at doses up to 100 mg/day. Both drugs have reasonably well established safety profiles because of their widespread use. Based on what is known about phentermine and topiramate as well as what was observed in the PHEN/TPM clinical development program, the following five safety concerns are highlighted.

Cardiovascular

Although phentermine was a component of the “phen-fen” (phentermine-fenfluramine) combination, which was linked to increased risk for cardiac valvulopathy, current evidence indicates that the valvulopathy was attributable to fenfluramine. Fenfluramine and its metabolite, norfenfluramine, are potent agonists of the 5HT_{2B} receptor. Activation of this serotonergic receptor is believed to represent the mechanism responsible for the valvulopathy associated with phen-fen.

In the 1-year safety cohort, palpitations were the most common treatment-emergent adverse event (TEAE) within the cardiac arrhythmia subclass and occurred with a higher frequency in PHEN/TPM-treated individuals (1.8%) compared to placebo (0.8%). Mean heart rate increased by 1.6 beats per minute in the high-dose PHEN/TPM-treated group compared to the placebo-treated group. A higher proportion of PHEN/TPM-treated individuals experienced a categorical increase in heart rate compared to placebo treated individuals (>20 bpm: 19.6% high-dose PHEN/TPM versus 11.9% placebo). The mean decreases in systolic and diastolic blood pressure (DBP) were greater in PHEN/TPM-treated individuals compared to placebo-treated individuals. Categorical increases in SBP and DBP were generally lower in the PHEN/TPM-treated group. Regarding cardiac ischemic events in the 1-year safety cohort, six individuals in the placebo group and five individuals in the PHEN/TPM group experienced a serious adverse event related to cardiac ischemia. The clinical significance of the observed vital sign changes with PHEN/TPM treatment in terms of hard cardiovascular outcomes in the overweight and obese population is unknown.

Suicidality

An FDA analysis of 199 pooled placebo-controlled trials of 11 (AED) antiepileptic drugs suggests that this class of drugs is associated with an increased risk of suicidality (OR 1.8, 95% CI: 1.2, 2.7). In the 1-year safety cohort from the PHEN/TPM development program, there were two reported events of suicidal ideation (one placebo and one PHEN/TPM). The Columbia-Suicide Severity Rating Scale (C-SSRS), a tool designed to prospectively assess for suicidality, was systematically administered in the PHEN/TPM Phase 3 clinical trials. There were no suicidal attempts, suicidal behaviors, or instances of serious suicidal ideation, as assessed by the C-SSRS. However the summary measure of suicidality occurred at a slightly higher frequency in the high-dose PHEN/TPM group (0.9%) versus placebo (0.7%).

Cognitive-related dysfunction

Topiramate at doses used for epilepsy and migraine prophylaxis is associated with cognitive-related adverse events, in particular, confusion, psychomotor slowing, difficulty with concentration and attention, memory impairment and language difficulties. A similar adverse event profile was demonstrated with PHEN/TPM treatment. In fact, there was a clear dose-related pattern of cognitive-related adverse events – i.e., disturbance in attention, memory, language - in the PHEN/TPM development program. When assessed as a group, the incidence of cognitive-related adverse events was 1.7%, 2.0%, 5.6%, and 7.8% in the placebo, low-dose, mid-dose, and high-dose PHEN/TPM groups, respectively. The most common adverse event related to cognitive dysfunction was disturbance in attention.

Metabolic acidosis

Prior clinical trials as well as PHEN/TPM clinical experience have determined that topiramate can cause metabolic acidosis in some patients through its mechanism of carbonic anhydrase inhibition. Approximately 30% of individuals treated with high-dose PHEN/TPM experienced a serum bicarbonate <21 mEq/L compared to 5.9% of individuals treated with placebo. Consequences of untreated chronic metabolic acidosis may include hyperventilation, fatigue, anorexia, and increased risk for osteomalacia or osteoporosis. PHEN/TPM is intended for chronic use and the long-term effect of low bicarbonate is unknown within this study population. Additionally, it will be important to determine how PHEN/TPM-induced metabolic acidosis affects bone growth before expansion of PHEN/TPM use into the obese pediatric population.

Pregnancy exposure

Topiramate is considered teratogenic based on reproductive toxicity studies in several species. The TOPAMAX label lists fetal malformations related to bone growth and development in mouse (primarily craniofacial defects), rat (limb malformations including ectrodactyly, micromelia, and amelia), and rabbit (primarily rib and vertebral malformations) occurring at clinically relevant doses for the listed indications of epilepsy and migraine treatment. The applicant conducted embryofetal development studies in rats and rabbits with the proposed combination of phentermine and topiramate. There were no drug-induced effects of combination phentermine plus topiramate treatment on embryofetal development in either rats or rabbits. However, the combination phentermine plus topiramate embryofetal development studies were not designed to assess toxicity at higher doses of topiramate, as the exposures in rat and rabbit were approximately equal to proposed clinical doses of PHEN/TPM.

Human pregnancy outcomes with topiramate exposure have been tracked in several pregnancy registries including the North American Antiepileptic Pregnancy Registry and UK Epilepsy and Pregnancy Registry. Topiramate monotherapy-exposed pregnancies in the North American registry had a higher prevalence of malformations (4.1%, 95% CI: 1.9, 7.6) compared to controls (1.6%, 95% CI: 1.5, 1.7). The UK registry reported a major congenital malformation rate of 4.8% (95% CI: 1.7, 13.3) from 70 pregnancies exposed to topiramate monotherapy of 200 mg and higher.

The FDA Adverse Event Reporting System (AERS) was mined for pregnancy adverse outcomes with topiramate and phentermine monotherapy which generated 130 reports, 64 of which were considered analyzable for topiramate monotherapy exposure. When information on dosing and

timing of exposure were known, the majority reported use of 200 mg/day or less (29/45; 64%) and exposure occurred within the first trimester (37/42; 88%). Of these 64 reports, 21 (32.8%) demonstrated craniofacial abnormalities and 19/64 (29.9%) demonstrated skeletal abnormalities. The malformation pattern observed with topiramate-exposed pregnancies from the AERS database is similar to the types of malformations seen in both the UK registry and reproductive toxicity studies.

There were 34 pregnancies in the PHEN/TPM clinical development program with an average gestational age at diagnosis of 5.4 weeks. Of the 18 pregnancies carried to term (an additional pregnancy is ongoing), newborn examinations did not reveal any major malformations. However, the occurrence of 34 pregnancies in a controlled clinical development program where enrollment required agreement for use of double barrier or oral contraceptive plus single barrier methods, as well as a negative pregnancy test at each study visit underscores the large potential for pregnancy exposure with QNEXA if approved for weight loss.

It is unknown if the doses of topiramate in PHEN/TPM appreciably increase the risk for congenital malformations.

Introduction

Product information

VI-0521 or QNEXA is a combination product containing proprietary formulations of immediate-release phentermine hydrochloride beads (PHEN) and modified-release topiramate beads (TPM). VI-0521/QNEXA capsules are referred to in this briefing document as PHEN/TPM. Four fixed-dose strengths are proposed PHEN/TPM 3.75/23 mg (low-dose), 7.5/46 mg (mid-dose), 11.25/69 mg (three-quarter-dose), and 15/92 mg (high-dose). The proposed treatment regimen starts with low-dose PHEN/TPM, up-titrating as tolerated to mid-dose PHEN/TPM, the recommended maintenance dose. Individuals not achieving adequate weight loss or improvements in weight-related co-morbidities on mid-dose are recommended to titrate up via the three-quarter PHEN/TPM dose to high-dose PHEN/TPM. In addition, the applicant considers low-dose PHEN/TPM as a treatment dose in some individuals based on individual treatment goals. Data presented in this New Drug Application (NDA) were submitted to support the following proposed indication by VIVUS, Inc.:

QNEXA is indicated for the treatment of obesity, including weight loss and maintenance of weight loss and should be used in conjunction with diet and exercise. QNEXA is recommended for:

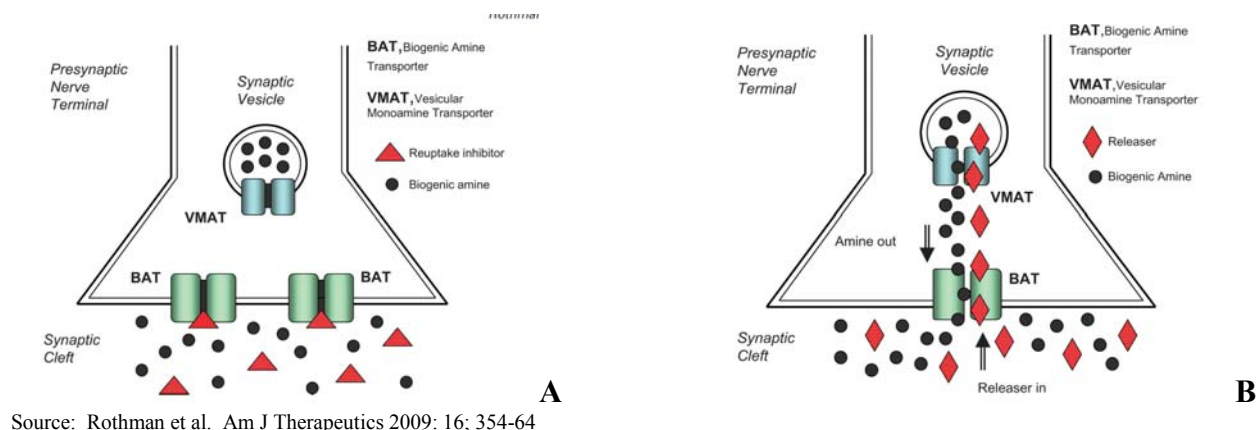
- *Obese patients ($BMI \geq 30 \text{ kg/m}^2$), or*
- *Overweight patients ($BMI \geq 27 \text{ kg/m}^2$) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity).*

Pharmacology

Amphetamines are appetite suppressants that interact with biogenic amine neurons in the central nervous system.¹ These neurons synthesize, store, and release amine transmitters, norepinephrine (NE), dopamine (DA), and serotonin (5-HT). Located on the plasma membranes of these neurons are distinct specialized transporter proteins that take up the previously released neurotransmitters [norepinephrine transporter (NET), dopamine transporter (DAT), serotonin transporter (SERT)] from the synaptic cleft. Appetite suppressants interact with these transporters as reuptake inhibitors or substrates. Reuptake inhibitors bind at the transporter and prevent the reuptake of the neurotransmitter from the synaptic cleft. Substrates also bind at the transporter but unlike the inhibitors are internalized by the neuron and cause a release of the respective neurotransmitter (Figure 1).

¹ Rothman et al. Appetite suppressants, cardiac valve disease and combination pharmacotherapy. Am J Therapeutics 2009; 16: 354-64

Figure 1: Mechanism of Reuptake inhibitors (A) and Substrates (B)



Amphetamine affects two neurotransmitters, dopamine and norepinephrine. Modifying the β -phenethylamine structure of amphetamine changes the effect on neurotransmitters (Figure 2). Phentermine which has an additional methyl group on the α -carbon atom of β -phenethylamine backbone is a cousin of amphetamine (Figure 3) and affects mainly norepinephrine release.

Figure 2: Amphetamine chemical structure

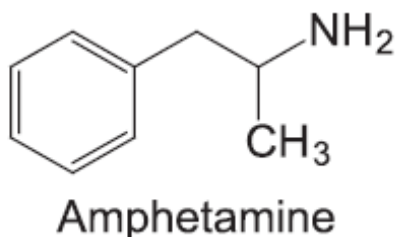
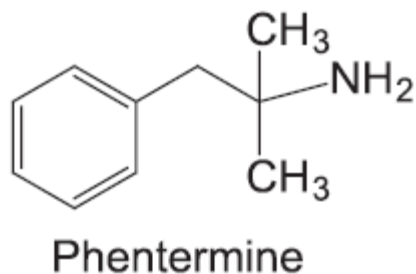


Figure 3: Phentermine chemical structure



Phentermine acts as a potent substrate at NET, and has weaker activity at DAT and SERT (Table 1). Phentermine-induced central norepinephrine release is its primary mechanism for inducing weight loss by reducing food intake.²

² Bray et al. Current and Potential drugs for treatment of obesity. Endocrine Reviews 1999; 20(6):805-75.

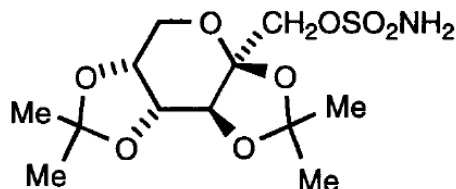
Table 1: Interaction of anorectic agents with neurotransmitter transporters

Test drug	Release NET* EC ₅₀ (nM ± SD)	NE uptake K _i (nM ± SD)	Release DAT* EC ₅₀ (nM ± SD)	DA uptake K _i (nM ± SD)	Release SERT EC ₅₀ (nM ± SD)	5-HT uptake K _i (nM ± SD)
(+)-Amphetamine	7.1 ± 0.9		24.8 ± 3.5		1765 ± 94	
Phentermine	39.4 ± 6.6		262 ± 21		3511 ± 253	
(-)-Ephedrine	43.1 ± 4.0		236 ± 9		>10,000	>50,000
(+)-Ephedrine	218 ± 14		2104 ± 68		Inactive	
Diethylpropion	>10,000	>10,000	>10,000	>10,000	>10,000	>10,000
N-ethylaminopropiophenone	99.3 ± 6.6			1014 ± 80	2118 ± 98	
Phendimetrazine	8300 ± 445	>10,000	19,000 ± 537	>10,000	>100,000	>100,000
(±)-Phenmetrazine	50.4 ± 5.4		131 ± 11		7765 ± 610	
(+)-Fenfluramine	302 ± 20			22000 ± 1100	51.7 ± 6.1	
(-)-Fenfluramine		7187 ± 559	>10,000	>20,000	147 ± 19	
(±)-Fenfluramine	739 ± 57			23700 ± 1300	79.3 ± 11.5	
(±)-Norfenfluramine	168 ± 17		1925 ± 295		104 ± 5	
(+)-Norfenfluramine	72.7 ± 5.4		924 ± 112		59.3 ± 2.4	
(-)-Norfenfluramine	474 ± 40			19194 ± 1048	287 ± 14	
(R,S)-sibutraminet		350		1200		2800
(R)-desmethylsibutraminet		4		12		44
(S)-desmethylsibutraminet		870		180		9200
(R)-didesmethylsibutraminet		13		8.9		140
(S)-didesmethylsibutraminet		62		12		4300

Source: Rothman et al. Am J Therapeutics 2009; 16; 354-64

Topiramate is a monosaccharide D-fructose derivative and contains a sulfamate group (Figure 4). Topiramate exhibits a combination of properties including modulatory effects on sodium channels, enhancement of GABA-activated chloride channels, inhibition of excitatory neurotransmission through actions on kainite and AMPA receptors, and inhibition of carbonic anhydrase (CA) isoenzymes in particular CA II and IV.³ The precise mechanism of topiramate's effect on weight is unclear.

Figure 4: Structure of topiramate



Currently commercially available products labeled for weight loss in United States

All prescription drugs currently approved for weight loss are anorectic agents, with the exception of orlistat (Table 2). Only orlistat and sibutramine are approved for long-term weight loss. Fenfluramine and dexfenfluramine were withdrawn from the market in 1997 due to concern for cardiac valvulopathy. Phentermine remained available in the United States after internal review by the FDA indicated that phentermine was unlikely to be causally related to valvulopathy.

³ Shank et al. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 2000; 41:S3-S9.

Phenylpropanolamine (PPA) containing nonprescription drugs such as Dexatrim were removed from the market in 2000 due to concern that PPA increased the risk for hemorrhagic stroke.

Table 2: FDA-approved products for weight management

Generic name	DEA schedule	Trade names	t _{1/2} (hr)	Tablet dosage	Daily dose range (mg)	Year original compound approved	Current Indication
Norepinephrine reuptake inhibitor							
Phentermine hydrochloride	IV	ADIPEX-P and generic	12-24	15, 30, and 37.5 mg	15-37.5	1959	Indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification, and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m ² , or ≥ 27 kg/m ² in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia).
Norepinephrine releasers							
Diethylpropion	IV	TENUATE and generic	4-6	25 mg	75	1959	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of 30 kg/m ² or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
Benzphetamine	III	DIDREX and generic	12	50 mg	25-150	1960	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of 30 kg/m ² or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
Phendimetrazine	III	BONTRIL; BONTRIL PDM; and generic	5-12	35 mg or 105 mg (extended release)	70-210	1959	Management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of 30 kg/m ² or higher who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
Serotonin-norepinephrine reuptake inhibitor							
Sibutramine	IV	MERIDIA	1.1	5, 10, 15 mg	5-15	1997	MERIDIA is indicated for the management of

Generic name	DEA schedule	Trade names	t _{1/2} (hr)	Tablet dosage	Daily dose range (mg)	Year original compound approved	Current Indication
							obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. MERIDIA is recommended for obese patients with an initial body mass index ≥ 30 kg/m ² , or ≥ 27 kg/m ² in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).
Lipase inhibitor							
Orlistat	Not scheduled	XENICAL	1-2	120 mg	120 mg TID	1999	ORLISTAT is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss . XENICAL is indicated for obese patients with an initial body mass index (BMI) ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).
		ALLI (Over-the-counter)	1-2	60 mg	60 mg TID	2007	<u>USE</u> For weight loss in overweight adults, 18 years and old, when used along with a reduced-calorie and low-fat diet
Source: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm							

Regulatory background

The active components of PHEN/TPM are phentermine hydrochloride and topiramate. Phentermine hydrochloride was approved by the FDA in 1959 as an appetite suppressant. Phentermine hydrochloride is available in the United States under the trade name Adipex-P® and the generic name of phentermine hydrochloride in oral capsule and tablet forms at 15, 30, and 37.5 mg. Topiramate was approved in 1996 for the treatment of seizures at doses up to 400 mg/day in adults and in 2004 for the prevention of migraine headaches at doses up to 100 mg/day. Topiramate is available in the United States under the trade name TOPAMAX® and the generic name of topiramate in oral capsule (15 mg and 25 mg) and tablet form (25, 50, 100, and 200 mg).

Division Guidelines for Developing Products for the Management of Obesity

PHEN/TPM was developed in accordance with the Division's 2007 draft Guidance for Developing Products for Weight Management.⁴ As outlined in that document, a weight-loss drug would be considered effective if after 1 year of treatment either of the following occurs:

- Mean: The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant.
- Categorical: The proportion of individuals who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

Guidelines for weight-management products used in combination

According to the draft weight-management guidance, the efficacy and safety of fixed-dose combination products for the management of obesity should be compared with the individual product components of the combination and placebo. A minimum difference in weight loss to establish superior efficacy between a fixed-dose combination and its individual component products has not been determined. However, the Division views more favorably a fixed-dose combination product that is associated with at least twice the weight loss observed with that of each of the individual components.

PHEN/TPM clinical development program

PHEN/TPM clinical database

The original NDA submission (28 December 2009) for the PHEN/TPM development program consisted of:

- 549 healthy individuals and 57 individuals with either hepatic or renal impairment from 10 completed Phase 1 studies
- 490 individuals from four completed Phase 2 studies
- 4510 from three completed Phase 3 studies

⁴ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf

Table 3: Phase 2 and Phase 3 trials: number of individuals randomized to placebo or PHEN/TPM

	Type of patient studies	Placebo	Dosage of PHEN/TPM			Total PHEN/TPM	Treatment duration (weeks)
			3.75/23	7.5/46	15/92		
OB-201	Obese	50	0	0	50 ^[1]	50	24 weeks
OB-202	OW/Obese type 2 DM	105	0	0	105	105	28 weeks
DM-230 ^[2]	OW/Obese type 2 DM	55	0	0	75	75	28 weeks
OB-205 ^[3]	OW/Obese	45	0	45	45	45	6 weeks
OB-301	Obese	109	0	107	108	215 ^[4]	28 weeks
OB-302	Obese	514	241	0	512	753	56 weeks
OB-303	Obese with co-morbidities	994	0	498	995	1493	56 weeks

[1] Includes doses of Phen 15 mg and TOPMAX 100 mg
[2] DM-230 and DM-231 were extension studies in which some individuals from OB-202 elected to continue in DM-230
[3] OB-205: Cross-over designed study
[4] Additional 432 individuals randomized to single-agent phentermine or topiramate
Source: Attachment 1, Pg 44, Type B pre-IND briefing document package 26 February 2010

PHEN/TPM Description of Phase 3 clinical trials

Three Phase 3 clinical trials, OB-301, OB-302, and OB-303 form the basis of the efficacy assessment of PHEN/TPM.

As shown in Table 4, all of these trials were randomized, double-blind, and placebo-controlled and included a combination of three fixed-dose formulations of PHEN/TPM with varying severity of weight-related co-morbidities. The three doses studied were 15/92 mg (high-dose), 7.5/46 mg (mid-dose), and 3.75/23 mg (low-dose).

Table 4: Description of Phase 3 trials

Study	Treatment groups	N Randomized	Age (years)	Population	Duration	Primary endpoint <u>Secondary/other endpoints</u>
OB-301	• Placebo	109	Adults ≤70	BMI ≥ 30 kg/m ² and ≤ 45 kg/m ² Type 2 diabetes excluded	28 weeks	• Weight loss at 28 weeks <u>Secondary</u> <ul style="list-style-type: none"> • % with 10% weight loss • Δ in waist circumference • Δ in IWQOL <u>Other</u> Δ in hunger and satiety, BP, lipids, HbA1c, fasting blood glucose, Framingham risk score
	• PHEN 7.5 mg	109				
		108				
	• PHEN 15 mg	108				
	• TPM 46 mg	107				
		107				
	• TPM 92 mg	108				
	• PHEN/TPM 7.5/46 mg					

Study	Treatment groups	N Randomized	Age (years)	Population	Duration	Primary endpoint <u>Secondary/other endpoints</u>
	<ul style="list-style-type: none"> PHEN/TPM 15/92 mg 					
OB-302	<ul style="list-style-type: none"> Placebo PHEN/TPM 3.75/23 mg PHEN/TPM 15/92 mg 	514 241 512	Adults ≤ 70	BMI ≥ 35 kg/m ² Type 2 diabetes excluded	56 weeks	<ul style="list-style-type: none"> Weight loss at 56 weeks <u>Secondary</u> <ul style="list-style-type: none"> Absolute weight loss % with 10% weight loss Δ in waist circumference <u>Other</u> Δ in BMI, BP, lipids, fasting glucose, Framingham risk score, fat and lean body mass by DEXA, hunger and satiety, IWQOL-Lite score, % with 15% weight loss
OB-303	<ul style="list-style-type: none"> Placebo PHEN/TPM 7.5/46 mg PHEN/TPM 15/92 mg 	994 498 995	Adults ≤ 70	BMI ≥ 27 kg/m ² and ≤ 45 kg/m ² Two or more weight-related co-morbidities	56 weeks	<ul style="list-style-type: none"> Weight loss at 56 weeks <u>Secondary</u> <ul style="list-style-type: none"> Absolute weight loss % with 10% weight loss Δ in waist circumference <u>Other</u> Δ in BMI, BP, lipids, fasting serum glucose, HbA1c, insulin, glucose and insulin by OGTT, Framingham risk score, hunger and satiety, IWQOL-Lite score, fat and lean body mass by DEXA, insulin resistance parameters, SF-36 scores, % with 15% weight loss

The primary efficacy endpoints for the three Phase 3 trials were percent weight loss at Week 28 or Week 56 and percentage of individuals with at least 5% weight loss at Week 28 or Week 56.

Additional secondary and other efficacy endpoints are listed below. Endpoints not in common with all three studies are followed in parentheses with the respective study(ies) in which the endpoint was measured.

Secondary efficacy endpoints included:

- Percentage of individuals with at least 10% weight loss at Week 28 or Week 56
- Change in waist circumference from baseline to Week 28 or Week 56
- Changes in Impact of Weight: Quality of Life questionnaire (IWQOL) composite and individual domain scores at Week 28 (OB-301)
- Absolute weight loss at Week 56 (OB-302, OB-303)

Other efficacy endpoints included changes from baseline in:

- Framingham 10-year risk assessment
- Lipids
- HbA1c (OB-301, OB-303)
- Fasting blood glucose
- Systolic and diastolic blood pressure
- Percent fat and lean body mass by DEXA (OB-302, OB-303)
- Body mass index (BMI) (OB-302, OB-303)
- Hunger and satiety by visual analog scale
- Glucose and insulin by oral glucose tolerance testing (OGTT) (OB-303)
- Insulin resistance parameters and fasting insulin (OB-303)
- SF-36 scores (OB-303)
- IWQOL-Lite questionnaire composite and individual domain scores (OB-302, OB-303)
- Percent achieving 15% weight loss (OB-302, OB-303)

Patient populations

OB-301: Adults ≤ 70 years of age with a BMI ≥ 30 kg/m² and ≤ 45 kg/m². Diabetic patients were excluded.

OB-302: Adults ≤ 70 years of age with a BMI ≥ 35 kg/m², triglyceride level ≤ 200 mg/dL either untreated or treated with a single antidyslipidemic agent, blood pressure $\leq 140/90$ mmHg either untreated or treated with up to two antihypertensive medications, and fasting serum glucose level ≤ 110 mg/dL. Diabetics were excluded. There was no upper limit exclusion criterion for BMI.

OB-303: Adults ≤ 70 years of age with a BMI ≥ 27 kg/m² and ≤ 45 kg/m² with two or more of the following obesity-related co-morbid conditions:

1. Hypertension (at least one of the following criteria)
 - a. Systolic blood pressure (SBP) ≥ 140 and ≤ 160 mmHg (≥ 130 and ≤ 160 mmHg, if diabetic)
 - b. Diastolic blood pressure (DBP) ≥ 90 and ≤ 100 mmHg (≥ 85 and ≤ 100 mmHg, if diabetic)
 - c. Requirement of two or more medications to achieve control (BP $< 140/90$ mmHg)
2. Hypertriglyceridemia

- a. Triglycerides (TG) ≥ 200 mg/dL and ≤ 400 mg/dL or requirement for two or more medications to achieve control (TG < 200 mg/dL)
 3. Metabolic derangements (at least one of the following)
 - a. Fasting blood glucose level > 100 mg/dL
 - b. Glucose level > 140 mg/dL at 2 hours during OGTT
 - c. Type 2 diabetes managed with lifestyle modification or metformin monotherapy
 4. Waist circumference ≥ 102 cm (40 in) for men or ≥ 88 cm (35 in) for women
- Individuals with a creatinine clearance < 60 ml/min were excluded. No lower limit on BMI was required for individuals with diabetes.

Pertinent exclusion criteria for Phase 3 trials (selected):

- Weight gain or loss of > 5 kg, use of a very-low-calorie diet, or participation in a formal weight loss program within the past three months
- Previous bariatric surgery
- Stroke, myocardial infarction, life-threatening arrhythmia, or coronary revascularization within the past 6 months
- Unstable angina, New York Heart Association Class II-IV congestive heart failure, or known or suspected clinically significant cardiac valvulopathy
- Cholelithiasis within the past 6 months
- Any history of nephrolithiasis
- Any history of bipolar disorder or psychosis, more than one lifetime episode of major depression, current moderate or severe depression (PHQ-9 score ≥ 10)
- Presence or history of suicidal behavior or ideation with some intent to act on it
- Antidepressant use that had not been stable for at least three months
- History of glaucoma or any past or present use of medications to treat increased intraocular pressure
- TSH > 1.5 x upper limit of normal (ULN), signs or symptoms of hypothyroidism, use of thyroid hormone treatment that was not stable for at least three months, or signs or symptoms of hypothyroidism
- Pregnancy, breastfeeding, or plans for pregnancy during the study period

Prohibited medications for Phase 3 trials:

- Anticonvulsants, including barbiturates, benzodiazepines, GABA analogues, hydantoins, phenyltriazines, succinimides, valproic acid and its derivatives, carbamazepine, zonisamide, and felbamate
- Tricyclic antidepressants, monoamine oxidase inhibitors, lithium, levodopa, and dopamine receptor agonists
- Insulins, incretins, thiazolidinediones
- Carbonic anhydrase inhibitors
- Chronic systemic glucocorticoid therapy
- Anti-obesity medications (prescribed or over-the-counter, including herbal preparations)

Restricted medications:

In individuals who developed a need for antidiabetic medications, metformin was the recommended first-line therapy, followed by α -glucosidase inhibitors and/or dipeptidyl peptidase-4 (DPP4) inhibitors.

Hormone replacement therapy (estrogen, thyroid, etc) or allowed antidepressants required stable doses for at least 3 months prior to screening.

Benzodiazepine and non-benzodiazepine sleep medications were permitted, if dosing had been stable for one month prior to screening, and frequency of use did not exceed twice a week.

Randomization and stratification

Requirements for randomization and receiving study drug included no clinically significant abnormalities on baseline physical exam, electrocardiogram (ECG) and laboratory results. Of importance, serum bicarbonate values had to be within normal limits, defined as 21-33 mEq/L, AST and ALT $<2.5\times$ ULN, TSH $\leq 1.5\times$ ULN, negative urine drug screen, and negative urine pregnancy test. In study OB-301, individuals also had to have fasting blood glucose levels ≤ 125 mg/dL. In study OB-302, fasting blood glucose had to be ≤ 110 mg/dL, and triglycerides ≤ 200 mg/dL.

OB-301 individuals were randomized to placebo, PHEN 7.5 mg, PHEN 15 mg, TPM 46 mg, TPM 92 mg, PHEN/TPM 7.5/46 mg, PHEN 15/92 mg in a 1:1:1:1:1:1 fashion and stratified by gender.

OB-302 individuals were randomized to placebo, PHEN/TPM 3.75/23 mg, or PHEN/TPM 15/92 mg in a 2:1:2 ratio and stratified by gender. At least 20% of individuals were to be male.

OB-303 individuals were randomized to placebo, PHEN/TPM 7.5/46 mg, or PHEN/TPM 15/92 mg in a 2:1:2 ratio. Randomization was stratified by gender and diabetic status, and at least 20% of individuals were to be male.

Study design

OB-301, OB-302, and OB-303 were all randomized, double-blind, placebo-controlled studies consisting of a 2-week screening period, 4-week titration period, and either a 24-week (OB-301) or 52-week (OB-302, OB-303) maintenance treatment period (Figures 5-7). During the titration period, doses were increased at weekly intervals for 4 weeks until the specified dose was reached.

If adverse events occurred that caused individuals to consider discontinuation or caused investigators to have medical concerns with continued dosing, investigators were permitted to suspend dosing for up to 7 days without discontinuing individuals from the study. Dose interruptions longer than 7 days were possible with agreement from the medical monitor. Individuals undergoing dose interruptions for any duration may have had the dose titrated back up to the original dose level based on discretion of the investigator. Individuals whose treatment had been interrupted or discontinued were encouraged to remain in the study and to attend their regularly scheduled study visits.

Lifestyle modification was advised for all randomized individuals using the LEARN Program for Weight Management developed by Kelly Brownell, PhD. Individuals were provided with a LEARN manual, and site personnel were encouraged to discuss the material at individuals' regularly scheduled visits.

Figure 5: OB-301 Study schematic

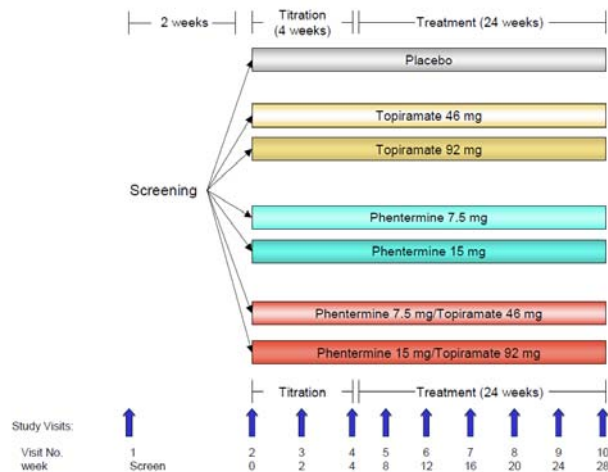


Figure 6: OB-302 Study schematic

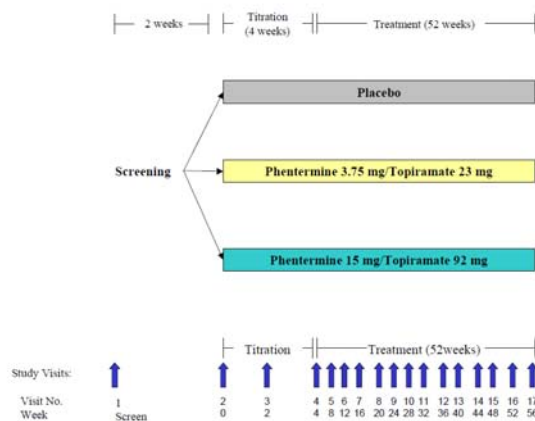
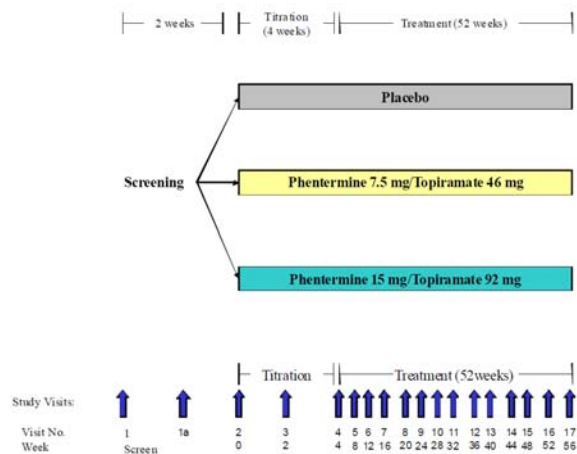


Figure 7: OB-303 Study schematic



Analysis Populations

- Randomized Set was defined as all individuals who were assigned randomly to treatment.
- Safety Set was defined as all randomized individuals who received at least one dose of study drug. The Safety Set was the primary analysis set for safety summaries.
- Intent-to-Treat (ITT) Set was defined as all randomized individuals who provided a baseline measurement (taken on or before the first dose date) of body weight, received at least one dose of study drug, and had at least one post-dose assessment of body weight. The ITT Set was the primary analysis set for efficacy summaries.
- Modified ITT (MITT) Set was defined as all randomized individuals who provided a baseline measurement (taken on or before the first dose date) of body weight, received at least one dose of study drug, and had at least one post-dose assessment of body weight within 7 days of the last dose of study drug.

Statistical considerations

According to the 2007 FDA's draft Guidance on Developing Products for Weight Management, the analysis of percentage weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model.⁵ The analysis should be applied to the **last observation carried forward (LOCF) on treatment** in the modified ITT population defined as individuals who received at least one dose of study drug and have at least one post-baseline assessment of body weight. The applicant's analysis used patients in the ITT population and carried forward the last observation regardless of study drug status (on drug or not on drug). The applicant also provided an analysis of percent weight loss in individuals who were actively taking study drug, a modified ITT analysis. The Division's statistical reviewer for PHEN/TPM, used the MITT population and carried forward the last observation while patients were on study drug. The results of the analysis for the two populations were very similar with approximately 0.3% more reduction in the on-drug (MITT LOCF) population than the applicant's ITT LOCF population analysis. Since there is no significant difference between the applicant's ITT LOCF population and Division's MITT LOCF population in the primary efficacy analysis, this briefing document will present the applicant's ITT LOCF analysis. Please review the Division's statistical analysis for further details on the MITT LOCF population efficacy results.

⁵ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf

Subject Demographics

In the 6-month OB-301 study ITT population, most participants were middle-aged, non-Hispanic, Caucasian women. At baseline, overall mean weight was 101.3 kg, mean BMI was 36.3 kg/m², mean SBP was 122.1 mmHg, and mean DBP was 79.1 mmHg. With the exception of race there were no statistically significant differences between treatment groups regarding demographic and baseline characteristics.

Table 5: Study OB-301 – Demographic and baseline characteristics – ITT set

Demographic/Baseline characteristics	Placebo N=103	PHEN 7.5 N=104	TPM 46 N=102	PHEN/TPM 7.5/46 N=103	PHEN 15 N=106	TPM 92 N=105	PHEN/TPM 15/92 N=103
Age (years) Mean (SD)	45.4 (11.5)	46.4 (11.5)	47.4 (12.4)	44.7 (11.1)	45.5 (12.3)	46.0 (11.2)	45.0 (12.8)
Gender (n, %) Male Female	23 (22.3) 80 (77.7)	22 (21.2) 82 (78.8)	22 (21.6) 80 (78.4)	22 (21.4) 81 (78.6)	22 (20.8) 84 (79.2)	22 (21.0) 83 (79.0)	22 (21.4) 81 (78.6)
Ethnicity (n, %) Hispanic or Latino Not Hispanic or Latino	11 (10.7) 92 (89.3)	8 (7.7) 96 (92.3)	11 (10.8) 91 (89.2)	10 (9.7) 93 (90.3)	9 (8.5) 97 (91.5)	6 (5.7) 99 (94.3)	8 (7.8) 95 (92.2)
Race (n, %) Caucasian Black Asian Other	79 (76.7) 23 (22.3) 0 0	78 (75.0) 24 (23.1) 2 (1.9) 2 (1.9)	89 (87.3) 11 (10.8) 2 (2.0) 2 (2.0)	78 (75.7) 24 (23.3) 0 0	88 (83.0) 14 (13.2) 1 (0.9) 1 (0.9)	81 (77.1) 21 (20.0) 2 (1.9) 0	86 (83.5) 13 (12.6) 2 (1.9) 2 (1.9)
Weight (kg) Mean (SD)	100.2 (13.1)	100.9 (15.3)	100.6 (16.4)	102.7 (16.4)	101.4 (16.3)	104.5 (15.7)	98.8 (14.7)
Height (cm) Mean (SD)	166.4 (8.8)	166.7 (9.0)	166.8 (8.8)	167.0 (8.4)	167.0 (8.6)	168.0 (8.5)	166.0 (8.6)
BMI (kg/m²) Mean (SD)	36.2 (4.0)	36.2 (4.0)	36.0 (4.1)	36.7 (4.0)	36.3 (4.2)	37.0 (4.3)	35.8 (3.8)
Waist circumference (cm) Mean (SD)	110.8 (9.6)	111.7 (11.0)	110.4 (11.6)	112.2 (12.8)	111.2 (11.2)	112.4 (11.0)	109.0 (10.1)
Systolic blood pressure (mmHg) Mean (SD)	120.5 (14.4)	121.7 (12.4)	123.9 (13.5)	123.5 (12.2)	120.5 (13.5)	123.4 (14.1)	121.6 (12.2)
Diastolic blood pressure (mmHg) Mean (SD)	78.6 (9.6)	78.5 (7.7)	79.1 (8.5)	80.3 (8.6)	78.3 (8.9)	80.9 (9.3)	78.0 (10.2)
Heart rate (bpm) Mean (SD)	72.1 (9.6)	73.2 (9.3)	72.3 (9.7)	73.0 (10.0)	72.6 (10.7)	73.4 (9.6)	72.7 (9.6)
Source: Applicant's Post-text Table 14.1.5 OB-301 CSR							

The majority of the individuals in the 1-year PHEN/TPM studies (OB-302 and OB-303) were middle-aged, non-Hispanic, Caucasian women (Table 6). Elderly individuals (≥ 65 years) represented less than 8% of the total study population. Approximately a third of individuals had extreme obesity (≥ 40 kg/m²). All of the studies occurred in the United States.

Table 6: Studies OB-302 and OB-303: Baseline subject demographics and characteristics – 1-year pooled PHEN/TPM data – ITT set

Demographic/Baseline characteristics	Parameter	Placebo N=1477	PHEN/TPM		
			3.75/23 mg N=234	7.5/46 mg N=488	15/92 mg N=1479
Age (years)	Mean (SD)	48.5 (11.4)	43.0 (11.1)	51.1 (10.4)	48.0 (12.0)
	Median	49.6	41.8	51.6	49.2
	(Min, Max)	18, 71	19, 70	21, 71	18, 71
Gender (n, %)	Male	375 (25.4)	40 (17.1)	147 (30.1)	385 (26.0)
	Female	1102 (74.6)	194 (82.9)	341 (69.9)	1094 (74.0)
Race (n, %)	Caucasian	1251 (84.7)	189 (80.8)	424 (86.9)	1235 (83.5)
	Black	199 (13.5)	35 (15.0)	51 (10.5)	210 (14.2)
	Asian	9 (0.6)	2 (0.9)	5 (1.0)	12 (0.8)
	Other	16 (1.1)	5 (2.1)	5 (1.0)	15 (1.1)
Ethnicity (n, %)	Hispanic or Latino	197 (13.3)	27 (11.5)	69 (14.1)	201 (13.6)
	Not Hispanic or Latino	1280 (86.7)	207 (88.5)	419 (85.9)	1278 (86.4)
Weight (kg)	Mean (SD)	107.5 (20.2)	118.6 (21.9)	102.8 (18.2)	107.1 (19.6)
Height (cm)	Mean (SD)	166.9 (9.6)	166.7 (8.5)	168.0 (9.8)	166.8 (9.3)
Waist circumference (cm)	Mean (SD)	115.8 (13.3)	121.2 (15.2)	112.7 (12.4)	115.5 (13.5)
BMI category (n, %)	<30 kg/m ²	71 (4.8)	0	33 (6.8)	71 (4.8)
	≥ 30 to <40 kg/m ²	904 (61.2)	91 (38.9)	344 (70.5)	887 (60.0)
	≥ 40 kg/m ²	502 (34.0)	143 (61.1)	111 (22.7)	521 (35.2)
Systolic blood pressure (mmHg)	Mean (SD)	126.6 (13.3)	122.5 (11.1)	128.5 (13.6)	125.9 (13.1)
Diastolic blood pressure (mmHg)	Mean (SD)	79.7 (9.0)	77.8 (7.5)	80.6 (8.7)	79.2 (8.8)
Heart rate (bpm)	Mean (SD)	72.5 (9.6)	72.3 (9.2)	72.2 (10.1)	72.8 (9.9)
Source: Applicant's Table 12, Pg 53; ISE					
Data from studies OB-302 and OB-303 are included					

Study OB-302 permitted enrollment of individuals with BMI's of 45 kg/m² and higher but excluded individuals with type 2 diabetes or uncontrolled weight-related co-morbidities. Study OB-303 sought to include individuals with weight-related co-morbidities and limited the BMI inclusion criteria. These differences in study populations explain the contrast between the two studies regarding BMI, fasting serum glucose, lipid parameters, and blood pressure at baseline (Table 7).

Table 7: Selected baseline characteristics of total population- Studies OB-302 and OB-303 – randomized set

Baseline characteristic	OB-302 Total population Mean (SD)	OB-303 Total population Mean (SD)
Body mass index (kg/m ²)	42.1 (6.2)	36.6 (4.5)
LDL-C (mg/dL)	121.0 (31.4)	123.1 (35.4)

Baseline characteristic	OB-302 Total population Mean (SD)	OB-303 Total population Mean (SD)
HDL-C (mg/dL)	49.5 (12.2)	48.9 (13.6)
TC (mg/dL)	194.1 (35.3)	204.5 (40.4)
TG (mg/dL)	116.5 (38.6)	162.5 (74.1)
Fasting serum glucose (mg/dL)	93.2 (9.1)	106.1 (22.2)
HbA1c (%)	ND	5.9 (0.8)
Systolic blood pressure (mmHg)	122.0 (11.4)	128.4 (13.5)
Diastolic blood pressure (mmHg)	77.4 (7.7)	80.6 (9.1)
ND: Not done		
Source: Applicant's post-text Table 14.1.4; OB-302, OB-303 CSR		

Medical history and concomitant medications

The majority (65.3%) of individuals in study OB-301 were non-smokers, 29% reported a history of hypertension and a quarter of individuals reported a history of dyslipidemia. At baseline 16.1% reported depression and 14.5% reported insomnia. Only two individuals reported a history of myocardial infarctions. During the double-blind treatment period, the most common types of concomitant medications were propionic acid derivatives (e.g. ibuprofen) (36.0%), anilides (e.g. Tylenol) (26.8%), and plain multivitamins (19.7%). Approximately 10% of individuals took statins; the percentage of individuals in the TPM 46 mg and PHEN 15 mg treatment groups who took statins was higher than in the other treatment groups. Approximately 7.6% of individuals were on thyroid hormone replacement therapy. Selective serotonin reuptake inhibitors (SSRIs) were taken by 11.6% of individuals and 6.6% were on other antidepressants such as bupropion.

In study OB-302, individuals had to have a fasting glucose ≤ 110 mg/dL, TG ≤ 200 mg/dL (allowed 1 lipid-lowering medication), and blood pressure $\leq 140/90$ mmHg (allowed up to two antihypertensive medications). Individuals with diabetes were excluded. The majority of individuals (66%) were non-smokers, a quarter of individuals reported hypertension, only five individuals reported a history of myocardial infarction, and approximately 20% reported abnormal lipids. At baseline 16% reported a history of depression and 9.6% were on selective serotonin reuptake inhibitors and 6.1% on other antidepressants such as bupropion. The majority of concomitant medications were propionic acid derivatives (e.g. ibuprofen) (31.2%), anilides (e.g. Tylenol) (22.5%), and multivitamins (16.0%). Less than 10% were on statins and thyroid hormone replacement therapy.

In comparison to the other Phase 3 studies, study OB-303 required individuals to have two or more weight-related co-morbidities. This explains the greater proportions of individuals in study OB-303 reporting hypertension (68.8%), history of myocardial infarction (1.5%), and abnormal lipids (57.2%). The most common medications were propionic acid derivatives (e.g. ibuprofen) (30.9%), statins (27.0%), multivitamins (24.2%). Approximately 52.5% individuals met the protocol-specified eligibility criteria for hypertension; 36.2% for hypertriglyceridemia; 15.8% for diabetes; and 66.8% for impaired glucose tolerance. The percentages of individuals with these co-morbidities were similar among the treatment groups. In total, 91.5% individuals had

two or more protocol-specified co-morbidities; 51.3% individuals had three or more co-morbidities; and 12.2% individuals had four co-morbidities.

Subject Disposition

There were two types of discontinuations defined within the PHEN/TPM Phase 3 trials. Individuals could (1) discontinue study drug but still remain in the study and attend follow-up visits or (2) withdraw all study participation. In study OB-301, 65.5% of individuals completed visits on study drug. Of the remaining 34.5%, a higher percentage of individuals on PHEN/TPM discontinued due to an adverse event compared to individuals treated with placebo or the individual components.

Table 8: Study OB-301 Subject disposition – randomized set

	Placebo N=109	PHEN 7.5 N=109	TPM 46 N=108	PHEN/TPM 7.5/46 N=107	PHEN 15 N=108	TPM 92 N=107	PHEN/TPM 15/92 N=108
Randomized	109 (100.0)	109 (100.0)	108 (100.0)	107 (100.0)	108 (100.0)	107 (100.0)	108 (100.0)
Completed study visits on study drug	69 (63.3)	74 (67.9)	72 (66.7)	73 (68.2)	72 (66.7)	67 (62.6)	68 (63.0)
Discontinued study drug	40 (36.7)	35 (32.1)	36 (33.3)	34 (31.8)	36 (33.3)	40 (37.4)	40 (37.0)
Main reason for discontinuation of study drug							
Adverse event	8 (7.3)	10 (9.2)	8 (7.4)	16 (15.0)	11 (10.2)	18 (16.8)	23 (21.3)
Lost to follow-up	12 (11.0)	13 (11.9)	11 (10.2)	6 (5.6)	7 (6.5)	8 (7.5)	9 (8.3)
Withdrew consent	9 (8.3)	7 (6.4)	6 (5.6)	4 (3.7)	8 (7.4)	5 (4.7)	3 (2.8)
Protocol non-compliance	1 (0.9)	1 (0.9)	3 (2.8)	1 (0.9)	2 (1.9)	1 (0.9)	4 (3.7)
Pregnancy	1 (0.9)	0	1 (0.9)	2 (1.9)	1 (0.9)	2 (1.9)	0
Requirement for restricted medication	0	0	2 (1.9)	0	0	0	0
Treatment unblinded by investigator	0	0	0	0	0	1 (0.9)	0
Other	9 (8.3)	4 (3.7)	5 (4.6)	5 (4.7)	7 (6.5)	5 (4.7)	1 (0.9)
Source: Applicant's Table 4, Pg 52; OB-301 CSR							

Table 9 lists the disposition of individuals in the 1-year pooled Phase 3 trials (OB-302, OB-303). More individuals on PHEN/TPM completed visits on study drug compared to placebo in the 1-year pooled cohort. As expected, individuals in the PHEN/TPM treatment groups discontinued less for lack of efficacy than the placebo treatment group. PHEN/TPM treatment groups had a higher incidence of discontinuations of study drug due to an adverse event than the placebo group.

Table 9: Subject disposition – 1-year pooled Phase 3 studies – randomized set

	Placebo N=1508 n (%)	PHEN/TPM		
		3.75/23 mg N=241 n (%)	7.5/46 mg N=498 n (%)	15/92 mg N=1507 n (%)
Randomized	1508 (100.0)	241 (100.0)	498 (100.0)	1507 (100.0)
Completed study visits	888 (58.9)	147 (61.0)	374 (75.1)	1073 (71.2)
Completed study visits on study drug	805 (53.4)	138 (57.3)	344 (69.1)	935 (62.0)
Complete study discontinuation	620 (41.1)	94 (39.0)	124 (24.9)	434 (28.8)
Study drug discontinuation	701 (46.5)	102 (42.3)	154 (30.9)	570 (37.8)
Main reason for discontinuation of study drug				
Adverse event	132 (8.8)	28 (11.6)	58 (11.6)	275 (18.2)
Lost to follow-up	215 (14.3)	27 (11.2)	41 (8.2)	115 (7.6)
Withdrew consent	225 (14.9)	28 (11.6)	34 (6.8)	108 (7.2)
Lack of efficacy	62 (4.1)	6 (2.5)	3 (0.6)	11 (0.7)
Protocol non-compliance	18 (1.2)	5 (2.1)	3 (0.6)	14 (0.9)
Requirement for restricted medication	17 (1.1)	0	5 (1.0)	6 (0.4)
Pregnancy	2 (0.1)	1 (0.4)	1 (0.2)	15 (1.0)
Other	30 (2.0)	7 (2.9)	9 (1.8)	26 (1.7)
Source: Applicant's Table 11, Pg 51 ISE Data from studies OB-302, and OB-303				

Study OB-301: fixed-dose combination versus individual components

Efficacy

A factorial study design is recommended for Phase 2 of clinical drug development. The applicant performed both a Phase 2 factorial design study (OB-202) using currently marketed products of (phentermine 15 mg administered in the morning and topiramate 100 mg in the evening) and a Phase 3 factorial design study (OB-301) using the to-be-marketed product.

Table 10 describes the results for percent weight loss at Week 28 (ITT LOCF) in study OB-301. All treatment groups had a statistically significant decrease in LS mean percent weight from baseline. The LS mean placebo-subtracted percent weight loss for mid-dose and high-dose PHEN/TPM was 6.8% and 7.5%, respectively. Treatment with PHEN/TPM resulted in an additional 3% weight loss compared to the individual components alone (Table 11). The differences between groups were statistically significant.

Table 10: Study OB-301 – Mean percent weight loss at Week 28 LOCF – ITT set

	Placebo N=103	PHEN 7.5 mg N=104	TPM 46 mg N=102	PHEN/TPM 7.5/46 mg N=103	PHEN 15 mg	TPM 92 mg	PHEN/TPM 15/92 mg
Baseline weight (kg) Mean (SD)	100.2 (13.2)	100.9 (15.3)	100.6 (16.4)	102.7 (16.4)	101.4 (16.3)	104.5 (15.7)	98.8 (14.7)
Mean (SD) % change	-1.5 (4.6)	-5.2 (5.5)	-4.9 (5.4)	-8.2 (6.9)	-5.8 (5.8)	-6.1 (6.0)	-9.0 (7.1)
Source: Table 8, Pg 60, OB-301 CSR							

Table 11: Study OB-301 – Difference in LS mean percent weight loss at Week 28 LOCF and treatment comparisons – ITT set

PHEN/TPM	LS Mean (SE) percent weight loss from baseline	Comparator	LS Mean (SE) percent weight loss from baseline	LS Mean (SE) difference 95% CI	p-value
PHEN/TPM 15/92 VS.	9.2 (0.61)	PHEN 15	6.1 (0.61)	3.2 (0.83) (1.5, 4.8)	0.0001
		TPM 92	6.4 (0.62)	2.8 (0.83) (1.1, 4.4)	0.0009
		Placebo	1.7 (0.61)	7.5 (0.83) (5.9, 9.1)	<0.0001
PHEN/TPM 7.5/46 VS.	8.5 (0.62)	PHEN 7.5	5.5 (0.61)	3.0 (0.83) (1.4, 4.6)	0.0003
		TPM 46	5.1 (0.61)	3.3 (0.83) (1.7, 5.0)	<0.0001
		Placebo	1.7 (0.61)	6.8 (0.83) (5.1, 8.4)	<0.0001
PHEN/TPM 7.5/46 VS.	8.5 (0.62)	PHEN 15	2.4 (0.82)	2.4 (0.82) (0.8, 4.0)	0.0037
		TPM 92	2.0 (0.83)	2.0 (0.83) (0.4, 3.6)	0.0150
Source: Applicant’s Table 9, Pg 62, OB-301 CSR Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline weight as a covariate.					

Sixty-two percent and 66% of mid- and high-dose PHEN/TPM-treated individuals, respectively, lost at least 5% of baseline body weight compared with approximately 16% of placebo-treated individuals (Table 12). In addition, a statistically significant higher proportion of individuals treated with PHEN/TPM achieved $\geq 5\%$ body weight loss compared the individuals treated with the individual components.

Table 12: Percentage of individuals with $\geq 5\%$ and $\geq 10\%$ weight loss at Week 28 LOCF – ITT set

	$\geq 5\%$ Weight loss (1 st endpoint)		$\geq 10\%$ Weight loss (2 nd endpoint)	
	Frequency	Placebo-subtracted difference (%)	Frequency	Placebo-subtracted difference
Placebo	15.5%	--	6.8%	--
PHEN 7.5	43.3%	27.8	12.5%	5.7
TPM 46	39.2%	23.7	18.6%	11.8
PHEN/TPM 7.5/46	62.1%*	46.6	38.8%*	32.0
PHEN 15	46.2%	30.7	20.8%	14.0
TPM 92	48.6%	33.1	23.8%	17.0
PHEN/TPM 15/92	66.0%*	50.5	40.8%*	34
Source: Applicant's Table 10, 11, Pg 65, 67 OB-301 CSR				
*Combination reached statistical significance against placebo and constituents				

Safety

Although not a requirement for approval of a fixed-dose combination product, the Division looks more favorably on combination products that exhibit a potentially meaningful improvement in the safety profile compared to the individual components. In addition, the applicant has theorized that some of the expected side effects of the two drugs alone may be “mitigated by oppositional pharmacodynamic effects associated with the other component.” In particular, the cognitive slowing observed with topiramate treatment may be lessened with co-administration of phentermine.

To that effect, Table 13 lists the treatment-emergent adverse events (TEAEs) occurring in OB-301 by system organ classification across all treatment groups. The nervous and psychiatric systems had equal or higher frequencies of TEAEs with both mid- and high-dose PHEN/TPM compared to the individual components or placebo. Additional organ classifications with this pattern included the gastrointestinal, general disorders, renal, and cardiac systems. In addition, of the TEAEs that occurred at a frequency of $\geq 5\%$ of individuals in any treatment group, headache, paraesthesia, dysgeusia, disturbance in attention, dry mouth, and nausea occurred more often in the PHEN/TPM groups compared with the component groups.

Table 13: Summary of treatment-emergent adverse events by system organ classification (SOC) – safety set

System organ class	Placebo N=109 n (%)	PHEN 7.5 N=109 n (%)	TPM 46 N=106 n (%)	PHEN/TPM 7.5/46 N=106 n (%)	PHEN 15 N=108 n (%)	TPM 92 N=107 n (%)	PHEN/TPM 15/92 N=108 n (%)
Infections and infestations	41 (37.6)	35 (32.1)	41 (38.7)	38 (35.8)	41 (38.0)	39 (36.4)	41 (38.0)
Nervous system disorders	27 (24.8)	24 (22.0)	41 (38.7)	43 (40.6)	22 (20.4)	39 (36.4)	53 (49.1)
Gastrointestinal disorders	24 (22.0)	26 (23.9)	35 (33.0)	37 (34.9)	31 (28.7)	34 (31.8)	44 (40.7)
General disorders and administration site conditions	15 (13.8)	20 (18.3)	20 (18.9)	22 (20.8)	17 (15.7)	15 (14.0)	29 (26.9)
Psychiatric disorders	15 (13.8)	11 (10.1)	18 (17.0)	18 (17.0)	17 (15.7)	19 (17.8)	27 (25.0)
Musculoskeletal and connective tissue disorders	23 (21.1)	19 (17.4)	19 (17.9)	19 (17.9)	14 (13.0)	13 (12.1)	16 (14.8)
Eye disorders	14 (12.8)	8 (7.3)	16 (15.1)	18 (17.0)	18 (16.7)	15 (14.0)	12 (11.1)
Respiratory, thoracic, and mediastinal disorders	19 (17.4)	13 (11.9)	12 (11.3)	12 (11.3)	11 (10.2)	6 (5.6)	22 (20.4)
Injury, poisoning, and procedural complications	14 (12.8)	14 (12.8)	8 (7.5)	6 (5.7)	14 (13.0)	13 (12.1)	10 (9.3)
Skin and subcutaneous tissue disorders	2 (1.8)	7 (6.4)	15 (14.2)	7 (6.6)	12 (11.1)	5 (4.7)	11 (10.2)
Reproductive system and breast disorders	2 (1.8)	7 (6.4)	6 (5.7)	8 (7.5)	10 (9.3)	3 (2.8)	5 (4.6)
Metabolism and nutrition disorders	7 (6.4)	5 (4.6)	9 (8.5)	2 (1.9)	5 (4.6)	6 (5.6)	6 (5.6)
Investigations	2 (1.8)	5 (4.6)	6 (5.7)	4 (3.8)	8 (7.4)	4 (3.7)	5 (4.6)
Immune system disorder	2 (1.8)	4 (3.7)	2 (1.9)	0	6 (5.6)	7 (6.5)	2 (1.9)
Vascular disorders	2 (1.8)	5 (4.6)	1 (0.9)	3 (2.8)	4 (3.7)	1 (0.9)	3 (2.8)
Renal and urinary disorders	1 (0.9)	4 (3.7)	1 (0.9)	4 (3.8)	2 (1.9)	2 (1.9)	4 (3.7)
Cardiac disorders	1 (0.9)	2 (1.8)	2 (1.9)	3 (2.8)	0	1 (0.9)	7 (6.5)
Ear and labyrinth disorders	3 (2.8)	2 (1.8)	1 (0.9)	0	3 (2.8)	3 (2.8)	3 (2.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.9)	1 (0.9)	1 (0.9)	2 (1.9)	2 (1.9)	0
Endocrine disorders	0	0	0	1 (0.9)	1 (0.9)	1 (0.9)	0
Blood and lymphatic system disorders	1 (0.9)	0	0	0	1 (0.9)	0	0
Hepatobiliary disorders	1 (0.9)	1 (0.9)	0	0	0	0	0

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QNEXA (phentermine/topiramate)

Source: Applicant's Table 56, Pg 116; OB-301 CSR

Based on the known safety profiles of phentermine and topiramate as reported in the literature and product labels, a set of adverse events was specified at the preferred term level, categorized, and summarized as six targeted medical event classes (TME). A complete listing of the preferred terms for each class and subclass are provided in Appendix A. Table 14 lists the TME by class and subclass for study OB-301, excluding the menstrual disorders TME class. Both the mid- and high-dose PHEN/TPM combination product had an equal or higher frequency of TMEs than the individual components in the psychiatric and cognitive disorder class.

Within the psychiatric disorder class there were four subclasses: sleep disorders, depression, anxiety, and suicide/self-injury. Sleep disorders, primarily insomnia, was higher for individuals treated with PHEN/TPM at both strengths, compared to individuals treated with placebo or the components. Mid-dose PHEN/TPM depression and anxiety events occurred with a lower frequency compared to topiramate and placebo. There was no meaningful difference in the incidence of depression comparing PHEN/TPM with the components or placebo. The high-dose PHEN/TPM treatment group reported a higher frequency of anxiety-related events at high-dose PHEN/TPM compared to placebo and component treatment groups. One subject treated with high-dose PHEN/TPM experienced a suicidal/self-injurious TME within study OB-301.

The cognitive disorder class was divided into 4 subclasses: attention, memory impairment, language, and other cognitive disorders. The attention subclass showed a consistent pattern: individuals treated with either strength of the PHEN/TPM product demonstrated a higher frequency of attention-related adverse events compared to individuals treated with placebo or the components. For the remaining subclasses, only the high-dose PHEN/TPM gave rise to a higher frequency of events compared to placebo.

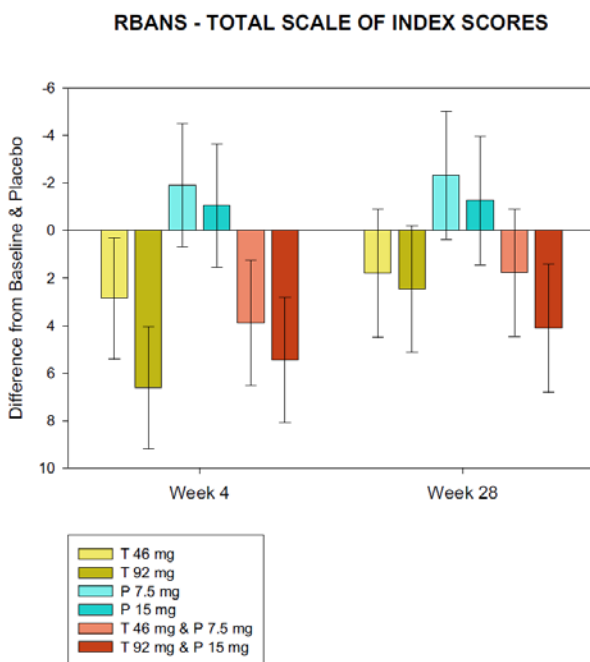
Table 14: Study OB-301: Summary of targeted medical events by class and subclass – safety set

CLASS	Subclass	Placebo N=109 n (%)	PHEN 7.5 N=109 n (%)	TPM 46 N=106 n (%)	PHEN/TPM 7.5/46 N=106 n (%)	PHEN 15 N=108 n (%)	TPM 92 N=107 n (%)	PHEN/TPM 15/92 N=108 n (%)
PSYCHIATRIC DISORDERS		16 (14.7)	13 (11.9)	16 (15.1)	21 (19.8)	16 (14.8)	17 (15.9)	29 (26.9)
	Sleep disorders	8 (7.3)	7 (6.4)	6 (5.7)	15 (14.2)	12 (11.1)	7 (6.5)	17 (15.7)
	Depression	8 (7.3)	2 (1.8)	5 (4.7)	4 (3.8)	8 (2.8)	10 (9.3)	8 (7.4)
	Anxiety	3 (2.8)	8 (7.3)	5 (4.7)	2 (1.9)	4 (3.7)	4 (3.7)	9 (8.3)
	Suicide/self-injury	0	0	0	0	0	0	1 (0.9)
COGNITIVE DISORDERS		3 (2.8)	2 (1.8)	8 (7.5)	8 (7.5)	2 (1.9)	7 (6.5)	9 (8.3)
	Attention	1 (0.9)	1 (0.9)	2 (1.9)	7 (6.6)	1 (0.9)	4 (3.7)	4 (3.7)
	Memory impairment	1 (0.9)	0	2 (1.9)	1 (0.9)	1 (0.9)	1 (0.9)	3 (2.8)
	Language	0	0	0	0	0	2 (1.9)	0
	Other cognitive disorders	2 (1.8)	1 (0.9)	4 (3.8)	0	0	2 (1.9)	3 (2.8)
OPHTHALMIC DISORDERS		4 (3.7)	0	4 (3.8)	3 (2.8)	6 (5.6)	3 (2.8)	2 (1.9)
	Ophthalmic disorders	4 (3.7)	0	4 (3.8)	3 (2.8)	6 (5.6)	3 (2.8)	2 (1.9)
PSYCHOMOTOR DISORDERS		1 (0.9)	1 (0.9)	2 (1.9)	0	1 (0.9)	0	2 (1.9)
	Psychomotor disorders	1 (0.9)	1 (0.9)	2 (1.9)	0	1 (0.9)	0	2 (1.9)
DRUG ABUSE/WITHDRAWAL		0	0	0	1 (0.9)	0	0	0
	Drug abuse	0	0	0	1 (0.9)	0	0	0
Source: Applicant's Table 59, Pg 123; OB-301 CSR								

To further assess the effect of the combination PHEN/TPM compared to components and placebo on cognitive function, the Repeatability Battery for the Assessment of Neuropsychological Status (RBANS) was performed at baseline, Week 4, and Week 28 or Early Termination. The RBANS is a battery of neuropsychological tests that measure five cognitive domains (immediate memory, visuospatial/constructional, language, attention, and delayed memory) with age-based index scores for each domain and a total scale score. Statistical analyses included differences from baseline and differences relative to placebo at Week 4 and 28. There were no formal analyses of between treatment group differences outside of comparisons with placebo. In general, the effects of the combination PHEN/TPM mirrored the effects observed with topiramate monotherapy. The main domain driving the overall Total Index Score was the Attention index.

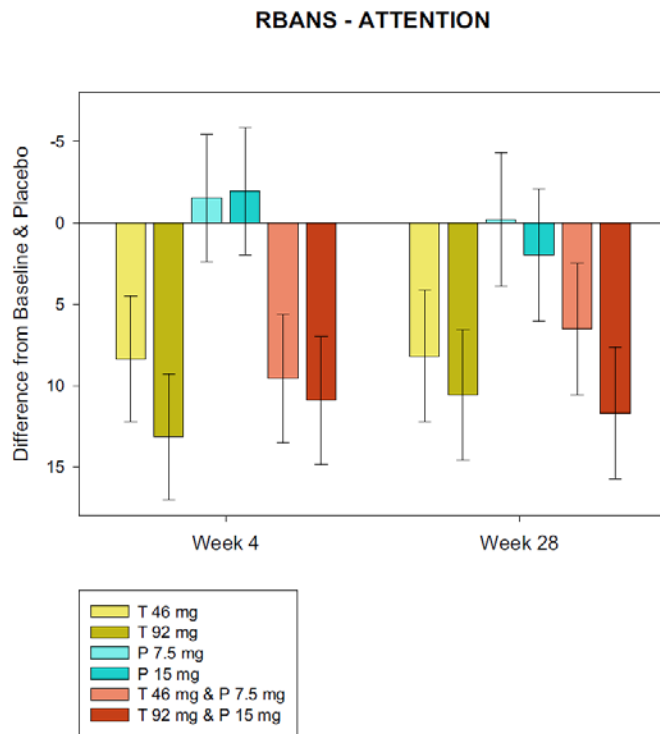
The following figures plot the placebo-subtracted treatment differences at Weeks 4 and 28 for the RBANS Total and domain scores. Confidence intervals not crossing zero represent a statistically significant difference from placebo. In the PHEN/TPM treated group, the Total Index score showed statistically significant impairment at Week 4 (both doses; $p < 0.01$) and at Week 28 (high-dose; $p < 0.01$) compared to placebo (Figure 8). Attention was impaired at Weeks 4 and 28 at both the mid- and high-dose PHEN/TPM compared to placebo ($p < 0.002$) (Figure 9). The Language Index score showed statistically significant impairment at Week 28 for both PHEN/TPM dosage strengths against placebo ($p < 0.01$) (Figure 10). Delayed Memory was statistically significantly different at Week 4 in the high-dose PHEN/TPM group compared to placebo ($p < 0.05$) (Figure 11). No effects were identified on the Immediate Memory and Visuospatial/Constructional Indices (Figures 12-13).

Figure 8: RBANS – Total scale of index scores: difference from baseline and placebo



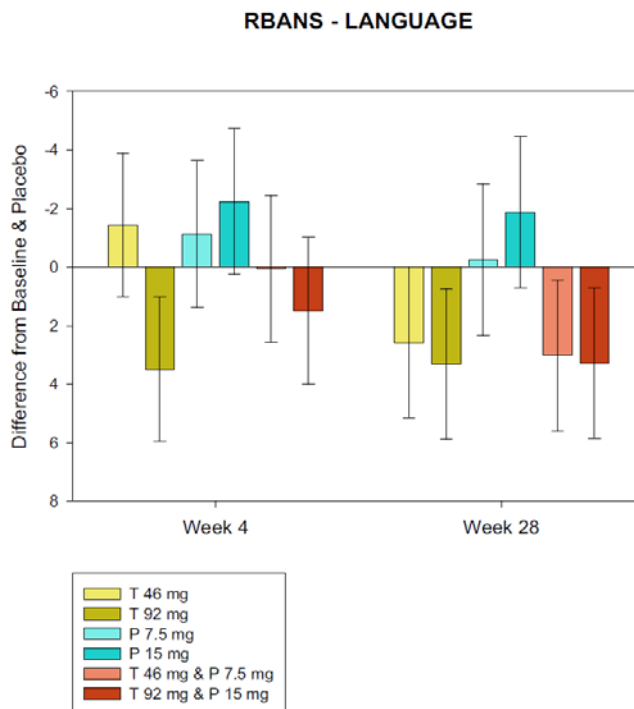
Source: Applicant's Figure, Pg 16, Section 16.1.13, OB-301 CSR
Bars are LS Means with 95% confidence intervals

Figure 9: RBANS – Attention index: difference from baseline and placebo



Source: Applicant's Figure, Pg 20, Section 16.1.13, OB-301 CSR
Bars are LS Means with 95% confidence intervals

Figure 10: RBANS – Language index: difference from baseline and placebo



Source: Applicant's Figure, Pg 19, Section 16.1.13, OB-301 CSR
Bars are LS Means with 95% confidence intervals

Figure 11: RBANS – Delayed memory index: difference from baseline and placebo

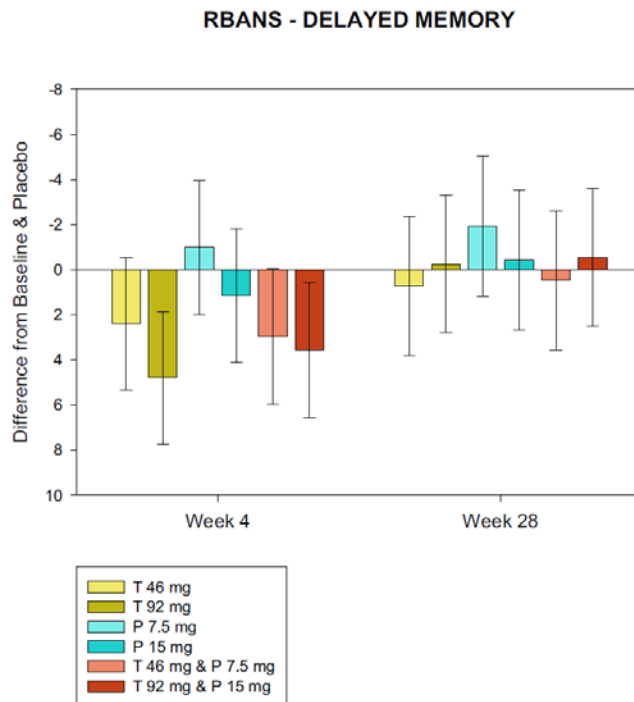


Figure 12: RBANS – Immediate memory index: difference from baseline and placebo

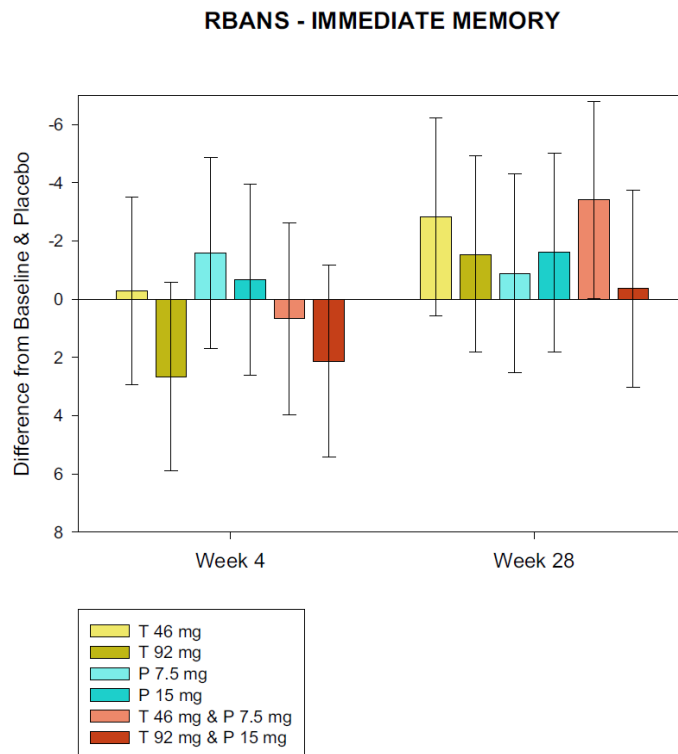
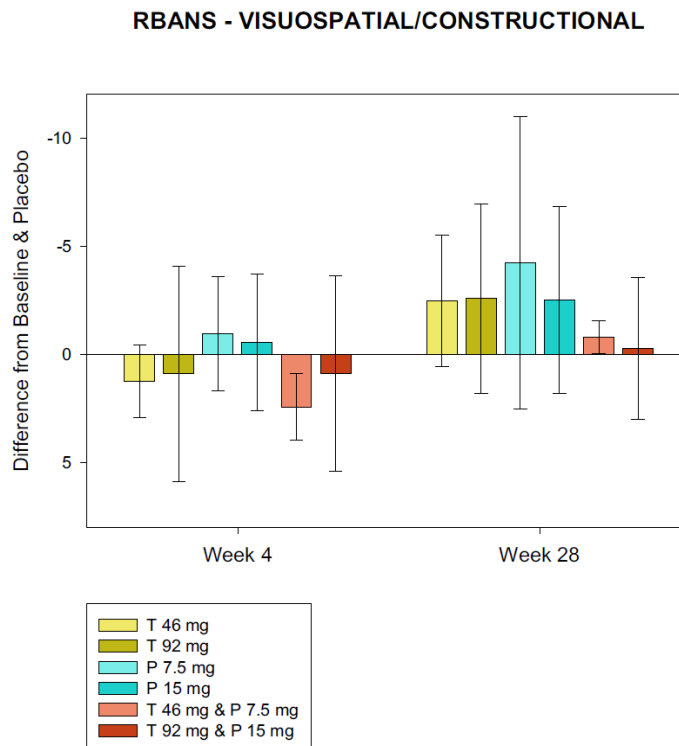


Figure 13: RBANS – Visuospatial/Constructional index: differences from baseline and placebo



Source: Applicant's Figure, Pg 21, Section 16.1.13, OB-301 CSR
Bars are LS Means with 95% confidence intervals

The translation of statistical significance to clinical relevance with RBANS testing may be evaluated by effect size. In an independent analysis commissioned by the applicant, an effect size of 0.5 was used as the minimum threshold for a clinically relevant change. Applying this measure, the four-week effect size of 0.42 on the Total Index Score for the high-dose PHEN/TPM would be considered borderline. Only the Attention index crossed this threshold at 0.58 and 0.66 in the mid- and high-doses, respectively at Week 4 and for the high-dose at 0.7 at Week 28.

Effect size is most meaningful when the testing outcome is the primary endpoint and the study is powered to ascertain the difference. Neither of these was true of study OB-301. Another approach used in this review to assess the clinical relevance of PHEN/TPM treatment on cognitive function was to evaluate RBANS outliers. The Division requested that the applicant provide the number and frequency of individuals who had a decrease of 1.5 standard deviations from baseline scores across treatment groups (Table 15). A 1.5 standard deviation decrement in function could be considered clinically relevant for an individual. For the Total Index Score a higher proportion of high-dose PHEN/TPM individuals experienced a 1.5 SD decrease compared to the other treatment groups. In the Attention domain, mid- and high-dose PHEN/TPM had a similar percentage of individuals with a 1.5 SD decrease.

Table 15: Study OB-301: Summary of individuals with a decrease of ≥ 1.5 standard deviations from baseline in RBANS total and domain scores

	Placebo N=85 n (%)	PHEN 7.5 N=88 n (%)	TPM 46 N=89 n (%)	PHEN/TPM 7.5/46 N=91 n (%)	PHEN 15 N=91 n (%)	TPM 92 N=94 n (%)	PHEN/TPM 15/92 N=95 n (%)
RBANS Total Score	0	0	2 (2.2)	0	0	3 (3.2)	5 (5.3)
Attention	2 (2.4)	0	8 (9.0)	8 (8.8)	1 (1.1)	15 (16.0)	8 (8.5)
Language	2 (2.4)	3 (3.4)	1 (1.1)	5 (5.5)	2 (2.2)	8 (8.5)	3 (3.2)
Delayed Memory	4 (4.7)	1 (1.1)	2 (2.2)	3 (3.3)	4 (4.4)	2 (2.1)	6 (6.3)
Immediate Memory	2 (2.4)	3 (3.4)	1 (1.1)	0	0	4 (4.3)	2 (2.1)
Visuospatial/Constructional	6 (7.1)	6 (6.8)	6 (6.7)	5 (5.5)	10 (11.1)	3 (3.2)	10 (10.5)

Source: Applicant's Table 84, Submission 22 Response to IR

In conclusion, relative to placebo, the RBANS study demonstrated that topiramate, given either alone or in combination with phentermine, produced statistically significant and clinically relevant negative effects on cognitive function, as assessed by the Total Index scores. Data from RBANS as well as the collected cognitive targeted medical events suggest that the addition of phentermine does not mitigate all of the cognitive effects of topiramate. However, the data suggest that the use of the mid-dose PHEN/TPM may have less of an effect on cognitive function than TPM 92 mg most likely related to the lower amount of topiramate.

Weight-related co-morbidities

The Division considers it beneficial if the fixed-dose combination product confers additional benefit on weight-related co-morbidities compared to therapy with the components. Study OB-301 evaluated several endpoints related to the co-morbidities observed in the overweight and obese population such as hypertension, dyslipidemia, and impaired glycemic control (Table 16).

Mid- and high-dose PHEN/TPM resulted in statistically significantly larger mean reductions in waist circumference compared with the components or placebo. A statistically significant treatment difference was observed between at least one dose of PHEN/TPM and one component or placebo for LDL-C, HbA1c, and SBP. There were no statistically significant treatment differences observed in Framingham 10-year risk score, percent change in HDL-C, percent change in total cholesterol, fasting blood glucose, and diastolic blood pressure between PHEN/TPM and the components or placebo. Although some treatment comparisons did not reach a nominal statistically significant treatment difference, mid- and high-dose PHEN/TPM treatment showed improvements in all the measured biomarkers of weight-related co-morbidities, aside from a small increase in triglycerides with mid-dose PHEN/TPM use.

Table 16: Study OB-301 – Change in secondary and other efficacy endpoints from baseline to Week 28 with LOCF and treatment comparisons – ITT set

Change in Waist circumference (cm)						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-8.7 (0.72)	-6.6 (0.71)	-2.2 (0.97)	(-4.1, -0.3)	0.0264
	TPM 92		-6.2 (0.72)	-2.5 (0.98)	(-4.4, -0.6)	0.0103

	Placebo		-3.3 (0.72)	-5.4 (0.98)	(-7.3, -3.5)	<0.0001
PHEN 7.5/46	PHEN 7.5	-8.8 (0.73)	-6.4 (0.72)	-2.3 (0.98)	(-4.3, -0.4)	0.0170
	TPM 46		-5.4 (0.72)	-3.4 (0.99)	(-5.3, -1.5)	0.0006
	Placebo		-3.3 (0.72)	-5.4 (0.98)	(-7.3, -3.5)	<0.0001
Change in Framingham 10-year risk						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-0.5 (0.19)	-0.1 (0.20)	-0.5 (0.26)	(-1.0, 0.1)	0.0856
	TPM 92		-0.2 (0.20)	-0.3 (0.26)	(-0.8, 0.2)	0.2144
	Placebo		-0.2 (0.20)	-0.4 (0.26)	(-0.9, 0.2)	0.1742
PHEN 7.5/46	PHEN 7.5	-0.4 (0.20)	-0.5 (0.20)	0.2 (0.27)	(-0.3, 0.7)	0.4725
	TPM 46		-0.2 (0.20)	-0.1 (0.27)	(-0.7, 0.4)	0.6371
	Placebo		-0.2 (0.20)	-0.2 (0.27)	(-0.7, 0.3)	0.4539
Percent change in LDL-C						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-9.4 (2.05)	-8.8 (2.10)	-0.6 (2.84)	(-6.2, 5.0)	0.8409
	TPM 92		-9.5 (2.08)	0.2 (2.82)	(-5.4, 5.7)	0.9571
	Placebo		-8.6 (2.13)	-0.7 (2.87)	(-6.4, 4.9)	0.8010
PHEN 7.5/46	PHEN 7.5	-14.3 (2.15)	-11.1 (2.11)	-3.2 (2.92)	(-8.9, 2.6)	0.2801
	TPM 46		-8.1 (2.12)	-6.2 (2.92)	(-11.9, -0.4)	0.0347
	Placebo		-8.6 (2.13)	-5.7 (2.93)	(-11.4, 0.1)	0.0538
Percent change in HDL-C						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	2.5 (1.54)	6.3 (1.57)	-3.8 (2.12)	(-8.0, 0.4)	0.0754
	TPM 92		-0.2 (1.57)	2.7 (2.11)	(-1.5, 6.8)	0.2077
	Placebo		0.4 (1.59)	2.2 (2.15)	(-2.1, 6.4)	0.3165
PHEN 7.5/46	PHEN 7.5	2.2 (1.58)	6.2 (1.58)	-4.0 (2.16)	(-8.2, 0.3)	0.0653
	TPM 46		0.5 (1.59)	1.7 (2.16)	(-2.5, 6.0)	0.4236
	Placebo		0.4 (1.59)	1.9 (2.17)	(-2.4, 6.1)	0.3858
Percent change in Total cholesterol						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-7.6 (1.38)	-6.2 (1.41)	-1.5 (1.91)	(-5.2, 2.3)	0.4418
	TPM 92		-8.0 (1.40)	0.3 (1.90)	(-3.4, 4.1)	0.8603
	Placebo		-6.2 (1.43)	-1.4 (1.92)	(-5.2, 2.4)	0.4591
PHEN 7.5/46	PHEN 7.5	-8.8 (1.41)	-8.1 (1.42)	-0.8 (1.94)	(-4.6, 3.0)	0.6954
	TPM 46		-6.3 (1.42)	-2.5 (1.94)	(-6.3, 1.3)	0.2021
	Placebo		-6.2 (1.43)	-2.6 (1.94)	(-6.4, 1.2)	0.1779
Percent change in triglycerides						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-8.8 (4.11)	-8.9 (4.20)	0.1 (5.68)	(-11.0, 11.3)	0.9856
	TPM 92		-4.5 (4.18)	-4.3 (5.65)	(-15.4, 6.8)	0.4477
	Placebo		3.8 (4.25)	-12.6 (5.73)	(-23.9, -1.4)	0.0277
PHEN 7.5/46	PHEN 7.5	2.2 (4.21)	-12.4 (4.22)	14.6 (5.78)	(3.2, 25.9)	0.0121

	TPM 46		-3.1 (4.26)	5.3 (5.77)	(-6.1, 16.6)	0.3629
	Placebo		3.8 (4.25)	-1.7 (5.79)	(-13.0, 9.7)	0.7740
Change in HbA1c (%)						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-0.0 (0.02)	0.1 (0.02)	-0.1 (0.03)	(-0.1, 0.0)	0.0050
	TPM 92		-0.0 (0.02)	-0.0 (0.03)	(-0.1, 0.0)	0.4519
	Placebo		0.1 (0.2)	-0.1 (0.03)	(-0.2, -0.1)	<0.0001
PHEN 7.5/46	PHEN 7.5	-0.0 (0.02)	0.1 (0.02)	-0.1 (0.03)	(-0.1, 0.0)	0.0014
	TPM 46		0.1 (0.02)	-0.1 (0.03)	(-0.1, 0.0)	0.0046
	Placebo		0.1 (0.02)	-0.1 (0.03)	(-0.2, -0.1)	0.0001
Change in fasting blood glucose (mg/dL)						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-1.2 (1.15)	-1.6 (1.14)	0.5 (1.56)	(-2.6, 3.5)	0.7729
	TPM 92		-0.5 (1.14)	-0.7 (1.56)	(-3.8, 2.4)	0.6530
	Placebo		-0.9 (1.15)	-0.3 (1.57)	(-3.4, 2.8)	0.8373
PHEN 7.5/46	PHEN 7.5	-0.8 (1.16)	-0.7 (1.14)	-0.1 (1.58)	(-3.2, 3.0)	0.9401
	TPM 46		-0.1 (1.14)	-0.7 (1.58)	(-3.8, 2.4)	0.6547
	Placebo		-0.9 (1.15)	0.0 (1.59)	(-3.1, 3.2)	0.9776
Change in systolic blood pressure (mmHg)						
		LS Mean (SE) change from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-5.2 (1.07)	-3.5 (1.07)	-1.7 (1.46)	(-4.6, 1.2)	0.2475
	TPM 92		-6.4 (1.07)	1.2 (1.46)	(-1.7, 4.1)	0.4114
	Placebo		-1.8 (1.07)	-3.4 (1.47)	(-6.2, -0.5)	0.0224
PHEN 7.5/46	PHEN 7.5	-7.0 (1.08)	-3.3 (1.07)	-3.8 (1.47)	(-6.6, -0.9)	0.0108
	TPM 46		-6.8 (1.08)	-0.3 (1.47)	(-3.1, 2.6)	0.8643
	Placebo		-1.8 (1.07)	-5.2 (1.47)	(-8.1, -2.3)	0.0004
Change in diastolic blood pressure (mmHg)						
		LS Mean (SE) from Baseline		Difference from comparator		
		Combination	Comparator	LS Mean (SE)	95% CI	p-value
PHEN 15/92	PHEN 15	-2.0 (0.77)	-0.9 (0.77)	-1.2 (1.05)	(-3.2, 0.9)	0.2705
	TPM 92		-3.9 (0.77)	1.8 (1.05)	(-0.2, 3.9)	0.0804
	Placebo		-0.7 (0.77)	-1.3 (1.05)	(-3.3, 0.8)	0.2242
PHEN 7.5/46	PHEN 7.5	-2.2 (0.77)	-1.5 (0.77)	-0.7 (1.05)	(-2.8, 1.4)	0.5147
	TPM 46		-2.6 (0.77)	0.4 (1.06)	(-1.7, 2.5)	0.7127
	Placebo		-0.7 (0.77)	-1.4 (1.05)	(-3.5, 0.6)	0.1724
Source: Applicant's Table 13, 31, 33, 35, 37, 39, 41, 43, 45, 47, Pg 69, 87, 89, 91, 93, 95, 97, 99, 101, 103; OB-301 CSR						
Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline as a covariate.						

Study OB-301 Conclusions

- Treatment with mid- and high-dose PHEN/TPM for 6 months led to statistically significant and clinically meaningful differences in the co-primary efficacy endpoints of percent weight loss and percentage of individuals with $\geq 5\%$ weight loss compared with the individual components of phentermine and topiramate.
-
- Mid- and high-dose PHEN/TPM resulted in statistically significant improvement in the secondary efficacy endpoint of waist circumference over the individual components and placebo.
- At least one dose of PHEN/TPM versus a component achieved a nominal statistically significant treatment difference for HbA1c, systolic blood pressure, and LDL-C.
- Mid- and high-dose PHEN/TPM did not demonstrate a statistically significant treatment difference compared to the individual components or placebo for change in Framingham 10-year risk score, percent change in HDL-C, percent change in total cholesterol, fasting blood glucose, or diastolic blood pressure.
- More individuals treated with PHEN/TPM discontinued due to an adverse event compared to individuals treated with the individual components.
- Both the mid- and high-dose PHEN/TPM product had an equal or higher frequency of TMEs than the individual components in the psychiatric and cognitive disorder class.
- Within the psychiatric and cognitive classes, sleep disorders, primarily insomnia, and attention-related adverse events were higher for individuals treated with PHEN/TPM products at both strengths, compared to individuals treated with the respective individual components.
- RBANS testing and adverse event reporting suggest that the topiramate component of PHEN/TPM is associated with negative effects on cognitive functioning relative to placebo and the effect is not entirely mitigated by phentermine co-administration

PHEN/TPM Weight loss efficacy at 1-year – Studies OB-302 and OB-303

Primary efficacy endpoint

Mid-and high-dose PHEN/TPM resulted in clinically and statistically significant changes in percent weight loss and the proportion of individuals achieving 5% or greater weight loss compared to placebo at 56 weeks. The LS mean placebo-subtracted percent weight loss for high-dose PHEN/TPM ranged from 8.6% to 9.4% (Table 17). Sixty-seven percent to 70% of the individuals treated with high-dose PHEN/TPM lost at least 5% of baseline body weight compared to 17% to 21% of individuals treated with placebo. In addition, a statistically significant proportion of individuals treated with high-dose PHEN/TPM lost 15% or greater of baseline body weight compared to placebo.

Table 17: Percent weight loss at Week 56 with LOCF and treatment comparisons – ITT set

Study	Treatment group	N	Baseline Mean (SD) Weight (kg)	Mean (SD) Percent Weight Loss (%) from Baseline	Difference from placebo		
					LS Mean difference	95% CI	p-value
OB-302 [1]	Placebo	498	115.7 (21.44)	1.6 (5.52)	--	--	--
	PHEN/TPM 3.75/23	234	118.6 (21.94)	5.1 (6.51)	3.5 (0.60)	(2.4, 4.7)	<0.0001
	PHEN/TPM 15/92	498	115.2 (20.83)	11.0 (9.42)	9.4 (0.48)	(8.4, 10.3)	<0.0001
OB-303 [2]	Placebo	979	103.3 (18.14)	1.8 (5.45)	--	--	--
	PHEN/TPM 7.5/46	488	102.8 (18.19)	8.4 (7.84)	6.6 (0.4)	(5.8, 7.4)	<0.0001
	PHEN/TPM 15/92	981	103.1 (17.64)	10.4 (8.51)	8.6 (0.33)	(8.0, 9.3)	<0.0001
Pooled OB-302, OB-303 [3]	Placebo	1477	107.5 (20.18)	1.7 (5.47)	--	--	--
	PHEN/TPM 3.75/23	234	118.6 (21.94)	5.1 (6.51)	3.2 (0.55)	(2.1, 4.3)	<0.0001
	PHEN/TPM 7.5/46	488	102.8 (18.19)	8.4 (7.84)	6.7 (0.4)	(6.0, 7.5)	<0.0001
	PHEN/TPM 15/92	1479	107.1 (19.62)	10.6 (8.83)	8.9 (0.27)	(8.3, 9.4)	<0.0001

Source: Applicant's Table 8, Pg 53, OB-302, CSR; Table 9, Pg 64 OB-303 CSR; Table 13, Pg 55 ISE;

[1] Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline weight as a covariate.

[2] 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 weight as a covariate.

[3] Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment, study, and gender as fixed effects and baseline as a covariate.

Table 18: Summary of the percentage of individuals with $\geq 5\%$, $\geq 10\%$, $\geq 15\%$ at Week 56 with LOCF – ITT set

Study	Treatment group	$\geq 5\%$ Weight loss (1° EP)		$\geq 10\%$ Weight loss (2° EP)		$\geq 15\%$ Weight loss (2° EP)	
		Frequency	Placebo-subtracted difference	Frequency	Placebo-subtracted difference	Frequency	Placebo-subtracted difference
OB-302	Placebo	17.3%	--	7.4%	--	3.4%	--
	PHEN/TPM 3.75/23	44.9%**	27.6	18.8%**	11.4	7.3%*	3.9
	PHEN/TPM 15/92	66.7%**	49.4	47.2%**	39.8	32.3%**	28.9
OB-303	Placebo	20.8%	--	7.4%	--	2.9%	--
	PHEN/TPM 7.5/46	62.1%**	41.3	37.3%**	29.9	19.3%**	16.4
	PHEN/TPM 15/92	70.0%**	49.2	47.6%**	40.2	28.8%**	25.9
Pooled OB-302, OB-303	Placebo	19.6%	--	7.4%	--	3.1%	--
	PHEN/TPM 3.75/23	44.9%**	25.3%	18.8%**	11.4%	7.3%*	4.2%
	PHEN/TPM 7.5/46	62.1%**	42.5%	37.3%**	29.9%	19.3%**	16.2%
	PHEN/TPM 15/92	68.9%**	49.3%	47.5%**	40.1%	30.0%**	26.9%
Source: Applicant's Table 11, 13, 16; Pg 66, 69, 74 OB-303 CSR, Applicant's Table 10, 12, 15; Pg 55, 57, 63 OB-302 CSR; Applicant's Table 15, Pg 58; ISE EP: Endpoint *p<0.05 **p<0.0001 compared to placebo							

Secondary and other efficacy endpoints

The table below describes the results for percent weight loss at Week 56 by baseline BMI in the 1-year cohort. Treatment with PHEN/TPM resulted in statistically significant greater LS mean percent weight loss compared to treatment with placebo.

Table 19: Percent weight loss from baseline and compared to placebo by baseline BMI at Week 56 with LOCF – ITT set

					Difference from placebo [1]		
Study	Treatment group	N	Baseline Mean (SD) Weight	Mean (SD) Percent Weight Loss (%) from baseline	LS Mean difference	95% CI	p-value
Pooled OB-302, OB-303	Baseline BMI <30 kg/m ²						
	Placebo	71	78.4 (8.95)	1.1 (4.46)	--	--	--
	PHEN/TPM 3.75/23	0	--	--	--	--	--
	PHEN/TPM 7.5/46	33	79.6 (9.51)	9.1 (6.45)	8.0 (1.34)	(5.3, 10.6)	<0.0001
	PHEN/TPM 15/92	71	80.9 (11.05)	9.1 (7.70)	8.0 (1.07)	(5.9, 10.1)	<0.0001
	Baseline BMI ≥30 kg/m ² and <40 kg/m ²						
	Placebo	904	100.4 (13.76)	1.8 (5.55)	--	--	--
	PHEN/TPM 3.75/23	91	104.0 (12.59)	5.6 (7.00)	3.6 (0.86)	(1.9, 5.2)	<0.0001
	PHEN/TPM 7.5/46	344	98.9 (14.06)	8.3 (8.12)	6.6 (0.48)	(5.7, 7.5)	<0.0001
	PHEN/TPM 15/92	887	99.6 (13.32)	10.3 (8.57)	8.5 (0.35)	(7.8, 9.2)	<0.0001
	Baseline ≥ 40 kg/m ²						
	Placebo	502	124.3 (18.82)	1.7 (5.45)	--	--	--
	PHEN/TPM 3.75/23	143	127.8 (21.63)	4.8 (6.18)	3.4 (0.75)	(1.9, 4.8)	<0.0001
	PHEN/TPM 7.5/46	111	121.5 (16.12)	8.4 (7.36)	6.4 (0.82)	(4.8, 8.0)	<0.0001
	PHEN/TPM 15/92	521	123.5 (17.82)	11.4 (9.35)	9.6 (0.47)	(8.7, 10.6)	<0.0001
Source: Applicant’s Tables 51, Post-text Tables 75- 77, Pgs 128, 350- 356; ISE [1] LS Mean, SE, 95% CI, and two-sided p-value are from an ANCOVA model with treatment and study as fixed effects and baseline as a covariate. All placebo comparisons are calculated as PHEN/TPM minus placebo.							

Body composition

Change in percent adiposity and lean body mass were measured by DEXA in a small subset of individuals in studies OB-302 and OB-303. Percent fat mass decreased and lean mass increased in all treatment groups, but only PHEN/TPM-treated individuals in study OB-303 achieved a nominally statistically significant difference over placebo (Table 20).

Table 20: Change in percent adiposity and lean body mass from baseline at Week 56 with LOCF by DEXA – ITT set

Study	Treatment group	Number of individuals	Percent Fat Body Mass		Percent Lean Body Mass	
			LS Mean (SE) change from baseline	p-value [2]	LS Mean (SE) change from baseline	p-value [2]
OB-302 [1]	Placebo	n=29	-1.7 (0.66)	--	1.6 (0.61)	--
	PHEN/TPM 3.75/23	n=14	-1.5 (0.95)	0.8541	1.3 (0.89)	0.7801
	PHEN/TPM 15/92	n=30	-3.3 (0.65)	0.0788	2.9 (0.60)	0.1171
OB-303 [1]	Placebo	n=42	-0.8 (0.52)	--	0.8 (0.49)	--
	PHEN/TPM 7.5/46	n=27	-2.9 (0.65)	0.0115	2.6 (0.62)	0.0223
	PHEN/TPM 15/92	n=60	-4.2 (0.44)	<0.0001	3.8 (0.41)	<0.0001

Source: Applicant's Tables 14.2.48, 14.2.49, Pgs 310, 313; OB-302 CSR and Applicant's Tables 14.2.82, 14.2.83, Pgs 505, 509; OB-303 CSR

[1] Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment as a fixed effect and baseline as a covariate

[2] Two-sided p-value is for treatment comparison of VI-0521 (PHEN/TPM) with placebo

Waist circumference and BMI decreased significantly in PHEN/TPM-treated individuals compared to placebo-treated individuals in a dose-related manner

Table 21: Change in waist circumference at Week 56 (LOCF) – ITT set

Waist circumference (cm)			
Study	Treatment group	LS Mean (SE) change from baseline	p-value [3]
OB-302 [1]	Placebo	-3.1 (0.47)	--
	PHEN/TPM 3.75/23	-5.6 (0.64)	0.0006
	PHEN/TPM 15/92	-10.9 (0.47)	<0.0001
OB-303 [2]	Placebo	-2.4 (0.3)	--
	PHEN/TPM 7.5/46	-7.6 (0.4)	<0.0001
	PHEN/TPM 15/92	-9.2 (0.3)	<0.0001

[1] Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline as a covariate.

[2] Least-squares mean, SE, 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.

[3] Two-sided p-value is for treatment comparison of VI-0521 (PHEN/TPM) with placebo.

Source: Applicant's Table 23, Pg 80; ISE

Table 22: Change in BMI from baseline to Week 56 (LOCF) – ITT set

Body mass index (kg/m ²)			
Study	Treatment group		
		LS Mean (SE) change from baseline	p-value [3]
OB-302 [1]	Placebo	-0.6 (0.16)	--
	PHEN/TPM 3.75/23	-2.1 (0.22)	<0.0001

Body mass index (kg/m ²)			
Study	Treatment group	LS Mean (SE) change from baseline	p-value [3]
	PHEN/TPM 15/92	-4.6 (0.16)	<0.0001
OB-303 [2]	Placebo	-0.5 (0.10)	--
	PHEN/TPM 7.5/46	-2.9 (0.14)	<0.0001
	PHEN/TPM 15/92	-3.7 (0.10)	<0.0001
[1] Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline as a covariate. [2] Least-squares mean, SE, 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. [3] Two-sided p-value is for treatment comparison of VI-0521 (PHEN/TPM) with placebo. Source: Applicant's Table 14, Pg 62; OB-302 CSR and Applicant's Table 15, Pg 73; OB-303 CSR			

Blood pressure

Systolic blood pressure decreased significantly in PHEN/TPM-treated individuals compared to placebo at all dose levels (Table 23). PHEN/TPM at low- and mid-doses did not obtain statistically significant decreases in DBP over placebo; however, high-dose PHEN/TPM did. In a subgroup of hypertensive individuals, mid- and high-dose PHEN/TPM treatment was associated with a significant reduction in SBP and DBP compared to placebo treatment.

Table 23: Changes in systolic and diastolic blood pressure at Week 56 (LOCF) – ITT set

Blood pressure (mmHg)					
Study	Treatment group	Systolic blood pressure		Diastolic blood pressure	
		LS Mean (SE) from baseline	p-value [3]	LS Mean (SE) from baseline	p-value [4]
OB-302 [1]	Placebo	0.9 (0.58)	--	0.4 (0.40)	--
	PHEN/TPM 3.75/23	-1.8 (0.79)	0.0019	-0.1 (0.55)	0.4257
	PHEN/TPM 15/92	-2.9 (0.57)	<0.0001	-1.5 (0.40)	0.0002
OB-303 [2]	Placebo	-2.4 (0.48)	--	-2.7 (0.32)	--
	PHEN/TPM 7.5/46	-4.7 (0.63)	0.0008	-3.4 (0.42)	0.1281
	PHEN/TPM 15/92	-5.6 (0.47)	<0.0001	-3.8 (0.32)	0.0031
OB-303 [3] (Hypertension subgroup [5])	Placebo	-4.9 (0.59)	--	-3.9 (0.38)	--
	PHEN/TPM 7.5/46	-6.9 (0.83)	0.0475	-5.2 (0.54)	0.0400
	PHEN/TPM 15/92	-9.1 (0.59)	<0.0001	-5.8 (0.38)	0.0003
[1] Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline as a covariate. [2] Least-squares mean, SE, 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. [3] Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment as a fixed effect and baseline as a covariate. [4] Two-sided p-value is for treatment comparison of VI-0521 (PHEN/TPM) with placebo. [5] Individuals defined at baseline with SBP ≥140 mmHg and ≤160 mmHg (≥130 mmHg and ≤160 mmHg if diabetic) or DBP ≥ 90 mmHg and ≤100 mmHg (≥85 mmHg and ≤100 mmHg if diabetic) or on two or more antihypertensive medications to achieve control Source: Applicant's Table 24, 25, Pg 82, 85; ISE					

Lipid parameters

Improvements in lipid parameters with PHEN/TPM were generally small with varying degrees of nominal statistical significance compared to placebo. High-dose PHEN/TPM treatment decreased LDL-C by 8.4% and 6.9% and increased HDL-C by 3.5% and 6.8% in study OB-302 and OB-303 respectively. Triglyceride levels showed the largest improvements with PHEN/TPM treatment aside from an increase in triglycerides with low-dose PHEN/TPM. Interestingly, the placebo-subtracted changes observed in a subgroup of hypertriglyceridemic individuals were similar to the changes observed in the whole population.

Table 24: Percent changes in lipid parameters at Week 56 (LOCF) – ITT set

Lipid parameters									
Study	Treatment group	LDL-C		HDL-C		Total cholesterol		Triglycerides	
		LS Mean % change (SE) from Baseline	p-value [4]	LS Mean % change (SE) from Baseline	p-value [4]	LS Mean % change (SE) from Baseline	p-value [4]	LS Mean % change (SE) from Baseline	p-value [4]
OB-302 [1]	Placebo	-5.5 (0.96)	--	-0.00 (0.83)	--	-3.5 (0.64)	--	9.1 (2.26)	--
	PHEN/TPM 3.75/23	-7.7 (1.29)	0.1338	0.5 (1.11)	0.7057	-5.4 (0.87)	0.0502	5.2 (3.05)	0.2639
	PHEN/TPM 15/92	-8.4 (0.94)	0.0157	3.5 (0.82)	0.0005	-6.0 (0.64)	0.0014	-5.2 (2.23)	<0.0001
OB-303 [2]	Placebo	-4.1 (0.87)	--	1.2 (0.66)	--	-3.3 (0.53)	--	4.7 (1.69)	--
	PHEN/TPM 7.5/46	-3.7 (1.14)	0.7391	5.2 (0.87)	<0.0001	-4.9 (0.70)	0.0345	-8.6 (2.22)	<0.0001
	PHEN/TPM 15/92	-6.9 (0.86)	0.0069	6.8 (0.65)	<0.0001	-6.3 (0.53)	<0.0001	-10.6 (1.67)	<0.0001
OB-303 [3] High TG subgroup [5]	Placebo	-3.6 (1.36)	--	2.8 (1.03)	--	-4.9 (0.74)	--	-8.8 (1.96)	--
	PHEN/TPM 7.5/46	0.7 (1.90)	0.0690	9.5 (1.44)	0.0002	-5.7 (1.04)	0.5149	-24.1 (2.74)	<0.0001
	PHEN/TPM 15/92	-4.3 (1.33)	0.7220	10.7 (1.01)	<0.0001	-7.8 (0.73)	0.0050	-25.6 (1.92)	<0.0001
<p>[1] Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline as a covariate</p> <p>[2] Least-squares mean, SE, 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.</p> <p>[3] Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment as a fixed effect and baseline as a covariate.</p> <p>[4] Two-sided p-value is for treatment comparison of VI-0521 (PHEN/TPM) with placebo.</p> <p>[5] Individuals defined at baseline with TG ≥200 mg/dL and ≤400 mg/dL; or on two or more lipid-lowering medications to achieve a TG <200 mg/dL</p> <p>Source: Applicant's Table 30-4, Pg 90, 94-97; ISE</p>									

Hemoglobin A1c and fasting serum glucose

Change in HbA1c for study OB-303 is presented in the table below. Study OB-302 did not assess the change in HbA1c. Treatment comparisons between PHEN/TPM and placebo groups achieved nominal statistical significance. The largest treatment difference (-0.3 %) was demonstrated in individuals with type 2 diabetes treated with mid and high-dose PHEN/TPM.

Table 25: Change in Hemoglobin A1c at Week 56 (LOCF) – ITT set

HbA1c (%)			
Study	Treatment group	Change at Week 56 (LOCF)	
		LS Mean (SE) from Baseline (%)	p-value [3]
OB-303 [1]	Placebo	0.1 (0.02)	--
	PHEN/TPM 7.5/46	-0.0 (0.02)	<0.0001
	PHEN/TPM 15/92	-0.1 (0.02)	<0.0001
OB-303 [2] (Diabetic subgroup)	Placebo n=144	-0.1 (0.07)	--
	PHEN/TPM 7.5/46 n=63	-0.4 (0.10)	0.0288
	PHEN/TPM 15/92 n=150	-0.4 (0.06)	0.0043
[1] Least-squares mean, SE, 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. [2] Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment as a fixed effect and baseline as a covariate. [3] Two-sided p-value is for treatment comparison of VI-0521 (PHEN/TPM) with placebo. Source: Applicant's Table 40, 42 Pg 102, 106; ISE			

Mid- and high-dose PHEN/TPM treatment resulted in a nominally significant decrease in fasting glucose compared to placebo. The largest treatment differences were observed in a subgroup of individuals with type 2 diabetes.

Table 26: Change in fasting serum glucose at Week 56 (LOCF) – ITT set

Fasting Serum Glucose (mg/dL)			
Study	Treatment group	LS Mean (SE) change from Baseline (mg/dl)	p-value [4]
OB-302 [1]	Placebo	1.9 (0.49)	--
	PHEN/TPM 3.75/23	0.8 (0.66)	0.1209
	PHEN/TPM 15/92	-0.6 (0.48)	<0.0001
OB-303 [2]	Placebo	2.3 (0.62)	--
	PHEN/TPM 7.5/46	-0.1 (0.80)	0.0047
	PHEN/TPM 15/92	-1.3 (0.61)	<0.0001
OB-303 (Diabetic subgroup) [3]	Placebo (n =153)	-5.6 (2.33)	--
	PHEN/TPM 7.5/46 (n=65)	-9.7 (3.57)	0.3325
	PHEN/TPM 15/92 (n=155)	-11.9 (2.32)	0.0556
[1] Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and gender as fixed effects and baseline as a covariate. [2] Least-squares mean, SE, 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.			

Fasting Serum Glucose (mg/dL)			
Study	Treatment group	LS Mean (SE) change from Baseline (mg/dl)	p-value [4]
<p>[3] Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment as a fixed effect and baseline as a covariate.</p> <p>[4] Two-sided p-value is for treatment comparison of VI-0521 (PHEN/TPM) with placebo.</p> <p>Source: Applicant's Table 41, 43, Pg 104, 107; ISE</p>			

PHEN/TPM one-year efficacy conclusions

- Low-, mid-, and high-dose PHEN/TPM versus placebo treatment was associated with statistically and clinically significant LS mean percent weight loss and proportion of individuals losing 5% or greater of body weight from baseline.
- Individuals treated with PHEN/TPM had a greater LS mean reduction in waist circumference of approximately 2.5 cm (low-dose) to 7.8 cm (high-dose) over placebo.
- Greater reductions in systolic and diastolic blood pressure were observed in individuals treated with PHEN/TPM versus placebo. However only treatment with high-dose PHEN/TPM compared with placebo was associated with a nominally statistically significant treatment difference of approximately 3 to 4 mmHg for systolic blood pressure and 1 to 2 mmHg for diastolic blood pressure.
- Mid- and high-dose PHEN/TPM treatment were associated with statistically significant decreases in total cholesterol and triglycerides and statistically significant increases in HDL-C compared to placebo. High-dose PHEN/TPM reduced LDL-C significantly over placebo by approximately 2.8%. There were no statistically significant improvements in lipid parameters in individuals treated with low-dose PHEN/TPM versus individuals treated with placebo. Overall the changes in lipid parameters with PHEN/TPM treatment were small.
- In study OB-303, there was a 0.1% reduction in HbA1c with high-dose PHEN/TPM compared to placebo. In a subset of overweight or obese individuals with type 2 diabetes at baseline, high-dose PHEN/TPM reduced HbA1c by 0.3% compared with placebo.

Safety profile characterization for phentermine and topiramate

Phentermine and topiramate are currently marketed drugs in the United States and have reasonably well established safety profiles. A summary of the individual safety profiles for phentermine and topiramate gleaned from product labeling and the literature and confirmed by a search of the FDA Adverse Event Reporting system (AERS) is outlined below.

Phentermine

The most prominent adverse events associated with phentermine relate to the central nervous and cardiovascular systems. Current phentermine labels include contraindications for advanced arteriosclerosis, cardiovascular disease, moderate- to-severe hypertension, hyperthyroidism, known hypersensitivity to sympathomimetic amines, glaucoma, agitation, history of drug abuse, and use of phentermine during or within 14 days of monoamine oxidase inhibitors. Other considerations include:

- **Pulmonary arterial hypertension (PAH)**

Pulmonary arterial hypertension is a rare condition characterized by elevated mean pulmonary arterial pressures.⁶ In the 1960s, there was an increase in cases of PAH in women taking the anorexigen aminorex. In the 1980s, the first cases of PAH associated with fenfluramine use were reported and additional cases were reported with the phen-fen combination for weight loss and dexfenfluramine in the 1990s.^{7,8,9} The International Primary Pulmonary Hypertension Study showed a significant association between PAH and use of appetite suppressants (phentermine was not included in this study).¹⁰ In a prospective surveillance study that collected information on patients diagnosed with pulmonary hypertension from 12 large referral centers in North America a strong association was observed between the use of fenfluramine for ≥ 6 months and the diagnosis of primary PAH, as compared to secondary pulmonary hypertension from an underlying medical condition (OR 7.5, 95% CI 1.7, 32.4). Importantly, there was no significant correlation with phentermine (OR 0.6, 95% CI 0.3-1.5).¹¹

- **Valvular heart disease**

In 1997, fenfluramine and dexfenfluramine were voluntarily withdrawn from the marketplace due to valvular heart disease observed in some patients receiving phen-fen or dexfenfluramine monotherapy.¹² Recent evidence supports the concept that valvular heart disease observed with fenfluramine use is due to agonist activity of its metabolite, norfenfluramine, at the 5HT_{2B} receptor.¹³ Review of the literature documented one case report attributing a tear in the bicuspid aortic valve of a young woman on phentermine. The authors stated that “phentermine is known to cause valvular disease with prolonged use” citing a meta-analysis by Sachdev et al.¹⁴ In a series of responses to this case report, Rothman and Hendricks refuted the cause of the valve tear as phentermine related.^{15,16} First, they pointed out the cited reference refers to the fenfluramine-induced valvulopathy and not phentermine. In addition, there are published reports demonstrating no evidence of valvulopathy with the use of phentermine alone or in combination with fluoxetine.^{17,18} More importantly, data support the concept that valvular heart disease

⁶ Ioannides-Demos et al. Safety of Drug Therapies used for weight loss and treatment of obesity. *Drug Safety* 2006; 29 (4): 277-302

⁷ Douglas JG et al. Pulmonary hypertension and fenfluramine. *BMJ* 1981; 283:881-3

⁸ Mark EJ et al. Fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. *NEJM* 1997; 337: 602-6.

⁹ Roche N et al. Pulmonary hypertension and dexfenfluramine [letter]. *Lancet* 1992;339:436-7.

¹⁰ Abenhaim L et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *NEJM* 1996; 335:609-16.

¹¹ Rich et al. Anorexigens and pulmonary hypertension in the United States: Results from the surveillance of North American pulmonary hypertension. *Chest* 2000; 117:890-74.

¹² Connolly et al. Valvular heart disease associated with fenfluramine-phentermine. *NEJM* 1997;337:581-588.

¹³ Rothman et al. Serotonergic drugs and valvular heart disease. *Expert Opin. Drug Safety* 2009; 8 (3):317-29.

¹⁴ Sachdev M et al. Effect of fenfluramine-derivative diet pills on cardiac valves: a meta-analysis of observational studies. *Am Heart J* 2002;144:1065-73

¹⁵ Rothman, RB, Hendricks EJ. Phentermine cardiovascular safety (letter to the editor) *Int J of Cardiology* 2009; doi:10.1016/j.ijcard.2008.12.205

¹⁶ Rothman RB, Hendricks EJ, Phentermine cardiovascular safety II: Response to Yosefy *Int J Cardiol.* 2009 Epub Mar 19, *Int J Cardiol* 2010; doi:10.1016/j.ijcard.2010.02.060

¹⁷ Bonow et al. 2008 Focused update Incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *JACC* 2008;52:e1-142

¹⁸ Whigham LD et al. Comparison of combinations of drugs for treatment of obesity: body weight and echocardiographic status. *Int J of obesity* 2007; 31: 850-57

observed with fenfluramine use is due to agonist activity at the 5HT_{2B} receptor.^{19,20} Other known valvulopathic drugs including ergotamine, methysergide, pergolide, and cabergoline are potent agonists of cardiac 5-HT_{2B} receptors.^{21,22,23} Phentermine is a weak serotonergic agent but assays have shown that phentermine does not have significant activity at the 5HT_{2B} receptor (Table 27).

In summary, neither mechanistic nor clinical evidence supports a causative role for phentermine in drug-induced valvulopathy.

Table 27: Interaction at 5HT receptors

Drug	Human 5-HT _{2A}	Human 5-HT _{2B}	Human 5-HT _{2C}
(±)-Fenfluramine	5216 ± 423	4134 ± 1281	3183 ± 637
(+)-Fenfluramine	11107 ± 2303	5099 ± 1173	6245 ± 874
(-)-Fenfluramine	5463 ± 600	5713 ± 2285	3415 ± 922
(±)-Norfenfluramine	2316 ± 278	52.1 ± 21	557 ± 61
(+)-Norfenfluramine	1516 ± 150	11.2 ± 7.3	324 ± 12
(-)-Norfenfluramine	3841 ± 614	47.8 ± 30.6	814 ± 98
Ergotamine	9.0 ± 1.0	3.0 ± 0.4	12 ± 1.5
Methysergide	15.0 ± 4.0	9.1 ± 4.9	1.8 ± 0.2
Methylergonovine	12.6 ± 1.0	0.49 ± 0.16	12.4 ± 1.0
Fluoxetine	299 ± 53	5030 ± 1960	50 ± 10
Norfluoxetine	638 ± 108	5063 ± 1974	286 ± 60
Trazodone	19.8 ± 2.4	73.6 ± 36	402 ± 44
m-CPP	391 ± 47	3.2 ± 1.0	59 ± 11
5-HT	614 ± 74	4.0 ± 1.9	12.2 ± 1.3
Phentermine	> 10,000	> 10,000	> 10,000

Source: Rothman et al. Expert Opin. Drug Saf 2009; 8 (3): 317-329

• Ischemic events

Noradrenergic stimulation can increase blood pressure via vasoconstriction and therefore it is of concern that use of phentermine may lead to an increase in ischemic events.

○ Cardiac

The New England Journal of Medicine published a letter to the editor of one otherwise healthy 35-year-old overweight (BMI 29 kg/m²) woman who experienced a myocardial infarction with acute ST-segment elevation associated with the use of phentermine.²⁴ The woman experienced hypotension, acute ST-segment elevation, and elevation of cardiac biomarkers (creatinine kinase level 445 U/L, troponin T level, 1.86 g/L) after induction of anesthesia for elective surgery.

¹⁹ Rothman et al. Serotonergic drugs and valvular heart disease. Expert Opin. Drug Safety 2009; 8 (3):317-29.

²⁰ Huang et al. Parallel functional activity profiling reveals valvulopathogens are potent 5-Hydroxytryptamine 2B receptor agonists: implications for drug safety assessment. Molecular Pharmacology 2009; 26 (4):710-22

²¹ Schade et al. Dopamine agonists and the risk of cardiac-valve regurgitation. NEJM 2007;356:29-38

²² Zanettini et al. Valvular heart disease and the use of dopamine agonists for parkinson's disease NEJM 2007;356:39-46.

²³ Roth et al. Drugs and valvular heart disease. NEJM 2007; 356:6-9

²⁴ Azarisman SM et al. Myocardial infarction induced by appetite suppressants in Malaysia (letter to the editor). NEJM 2007; 357; 1873-74.

Echocardiogram revealed septal hypokinesia. Angiography revealed normal coronary arteries. Past medical history was significant for mild intermittent asthma, but no recent use of bronchodilators. She was a non-smoker and had undergone two previous liposuction procedures. She reported intermittent phentermine (dose not reported) use in the past and for three consecutive days before her admission for elective surgery. Investigations to rule out cocaine abuse, viral myocarditis, aortic dissection, hypercoagulable states, and autoimmune vasculitis were negative.

In 2008, a case report of a 48-year-old woman with no previous cardiac disease history who presented with ventricular tachycardia/fibrillation associated with use of phentermine (dose unknown) was published.²⁵ Blood work showed a peak creatinine kinase of 716 U/L with a peak creatinine kinase-MB fraction of 36.1 U/L and a troponin I level of 17.9 ng/mL. Drug screen was negative. Left ventricular ejection fraction was 35% with mild diffuse nonobstructive coronary artery disease by coronary angiography. An echocardiogram revealed septal, anterior wall, and apical hypokinesia. On telemetry, the patient continued to exhibit ectopy with episodes of nonsustained ventricular tachycardia for more than 72 hours after her myocardial infarction. An electrophysiology study performed 5 days after presentation demonstrated an inducible sustained ventricular tachycardia. The patient subsequently received an implantable cardiac defibrillator.

○ **Central nervous system**

Two patients have been reported in the literature with cerebral ischemic events and use of phentermine with and without phendimetrazine.²⁶ One, a 41-year-old woman with multiple confounding factors such as cigarette smoking, hypertension, hypercholesterolemia, hypothyroidism, oral contraceptive use, and family history of vascular disease, suffered a cerebral infarct and vasculopathy. She had been taking phentermine and phendimetrazine (doses unknown) for 8 months and until two days before onset of her symptoms. The second patient was a 37-year-old woman who developed headache and left-sided face and arm numbness for 1 week after recent (duration unknown) consumption of phentermine (dose unknown) for weight loss. The authors concluded that a very small, deep cerebral or brain stem infarct in the ascending sensory pathway was the explanation for the second patient's sensory disturbance, however the cerebral MRI, cardiac ECHO, cerebral angiography, and laboratory values were negative.

○ **Gastrointestinal**

A case report of a 56-year-old woman presenting with nausea, bilious vomiting, and bright red blood per rectum was reported as associated with phentermine use.²⁷ The patient had been taking phentermine resin 15 mg twice daily over 10 weeks. Blood chemistry and coagulation profiles were normal. Stool examination for pathogens and *Clostridium difficile* toxin were negative. Biopsies of the colon were consistent with acute and chronic ischemic colitis. The family history was significant for the patient's mother being diagnosed with left-sided ulcerative colitis.

²⁵ Makaryus et al. Case report: Cardiac arrest in the setting of diet pill consumption. *Am J of Emergency Medicine* 2008; 26, 732.e1—732.e3

²⁶ Kokkinos J et al. Possible association of ischemic stroke with phentermine. *Stroke* 1993;24:310-313.

²⁷ Cornay et al. Ischemic colitis after weight-loss medication. *Can J Gastroenterol* 2003;17 (12):719-21

○ Ophthalmic

A case was reported in 1993 of an obese 35-year-old woman who developed an acute visual field defect in her left-eye after taking Adipex-P (phentermine hydrochloride) 37.5 mg daily for two days.²⁸ Medical history was negative for heart disease, diabetes, hypertension, hypercholesterolemia, or stroke. Investigation for autoimmune disorders, hypercoagulable states, stroke, genetic mutations, and infections were negative. Three weeks after discontinuing the medication the visual acuity in the left-eye had improved. Disc hemorrhages had resolved and the left optic disc had mild temporal pallor. The authors concluded the unilateral visual loss was attributable to ischemia of the posterior ciliary arteries of the left eye from vasoconstriction secondary to phentermine.

● Drug abuse and dependence/overdosage

As mentioned previously, phentermine is related chemically and pharmacologically to amphetamines. In a study by Griffiths et al. the reinforcing potency of anorectics was compared to their effects on reducing food intake in baboons.²⁹ The resulting anorectic-reinforcement ratios (Column F) are presented in Table 28. Phentermine was associated with a relatively low anorectic-reinforcement ratio compared to amphetamine.

Table 28: Anorectic-reinforcement ratio of anorectic drugs

Table I. Anorectic-Reinforcement Ratio of Eight Phenylethylamine Anorectic Drugs and Cocaine^a

A	B	C	D	E	F
Drug	Lowest reinforcing dose in baboon (mg/kg per infusion)	Dose suppressing baboon food intake 50% (mg/kg per day)	Ratio $\frac{C}{B}$	Lowest recommended human anorectic dose (mg/day)	Ratio $\frac{E}{B}$
Cocaine	0.03	16.0	14.81	—	—
Diethylpropion	0.5	22.0	1.22	75	0.75
<i>d</i> -Amphetamine	0.05	1.8	1.0	10	1.0
Phenmetrazine	0.5	7.4	0.41	50	0.50
Chlorphentermine	2.5	20.3	0.23	77.9	0.16
Phentermine	0.5	3.7	0.21	18.7	0.19
Clortermine	3.0	21.0	0.19	50	0.08
Fenfluramine	∞	7.0	0	60	0
Phenylpropanolamine	∞	48.1	0	75	0

^aCalculation of doses is described in text. All doses are expressed on the basis of the hydrochloride salts except for *d*-amphetamine which is expressed as the sulfate. To facilitate comparison, ratios were adjusted to an arbitrarily assigned *d*-amphetamine value of 1.0.

Source: Griffiths et al. Biol Psychiatry 1978

There are several case reports in the literature of psychosis associated with phentermine usage at 30 mg/day up to 180 mg/day.^{30,31,32,33} One of the first case reports involving phentermine overdosage (1964) was of an acute psychotic reaction following intentional ingestion of eight

²⁸ Chan JW et al. Acute nonarteritic ischemic optic neuropathy after phentermine. Eye 2005; 19; 1238-9

²⁹ Griffiths RR et al. Relationship between anorectic and reinforcing properties of appetite suppressant drugs; implications for assessment of abuse liability. Biol Psychiatry. 1978;13 (2): 283-290.

³⁰ Hoffman BF. Diet pill psychosis. CMA Journal. 1997; 116; 351-3.

³¹ Devan GS. Phentermine and psychosis. British Journal of Psychiatry 1990; 156; 442-3.

³² Cleare AJ. Phentermine, psychosis, and family history. J Clin Psychopharm 1996; 16 (6) 470-1.

³³ Lee SH et al. Schizophreniform-like psychotic disorder induced by phentermine: A case report. Chin Med J. 1998; 61:44-7.

Ionamin (phentermine resin) 30 mg capsules in a 26-year-old Caucasian woman with a history of mental illness.³⁴ Previous to the reported episode, the patient had been mentally stable without medications for 8 months, was working, and was engaged to be married. Her presenting symptoms included a hyperagitated state, with flight of ideas, tachycardia, dilated pupils, and extreme restlessness. She was treated as an outpatient and regained baseline mental status over the next two weeks.

Topiramate

Central nervous system related adverse events are frequently reported with topiramate use. The current TOPAMAX label includes warnings and precautions for acute myopia and secondary angle closure syndrome (glaucoma), oligohydrosis/hyperthermia, suicidal behavior and ideation, metabolic acidosis, and cognitive/neuropsychiatric events, sudden death associated with epilepsy, hyperammonemia and encephalopathy, kidney stones, and paresthesias.

- **Cognitive-related dysfunction**

Cognitive adverse events are associated with topiramate use, in particular confusion, psychomotor slowing, difficulty with concentration and attention, memory impairment, and language (word-finding difficulties). The TOPAMAX label reports that approximately 19% of patients with epilepsy in a topiramate monotherapy controlled trial experienced one or more cognitive-related adverse reactions on TOPAMAX 50 mg daily. In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse reactions was 19% for TOPAMAX 50 mg/day, 22% for 100 mg/day, 28% for 200 mg/day, and 10% for placebo.

- **Somnolence/Fatigue**

According to the TOPAMAX label, in individuals with epilepsy on TOPAMAX monotherapy, the incidence of somnolence was dose-related (9% for the 50 mg/day group and 15% for the 400 mg/day group) and the incidence of fatigue was comparable in both treatment groups (14% each). For the migraine population, fatigue and somnolence were dose-related and more common in the titration phase.

- **Suicidal Behavior and Ideation**

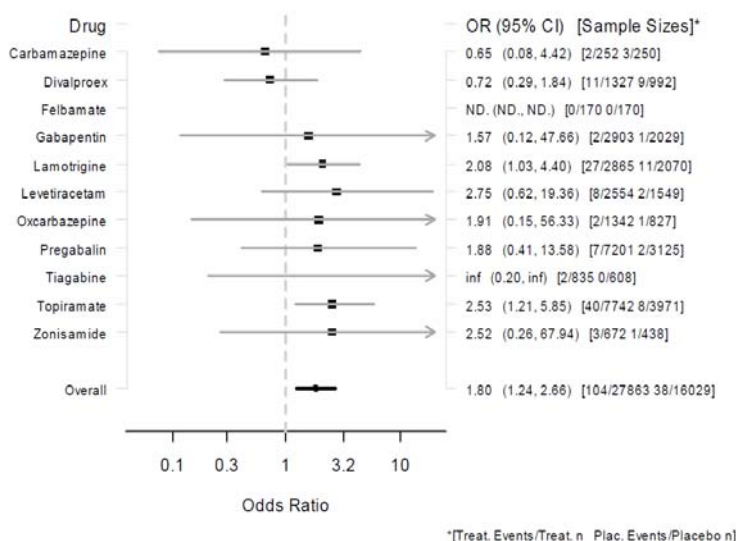
In an FDA analyses of 199 pooled placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs, including topiramate, patients randomized to one of the AEDs had a statistically significant increased risk of suicidal behavior or ideation relative to placebo (odds ratio 1.8, 95% CI:1.2, 2.7).³⁵ In these trials, which had a median treatment duration of 12 weeks and assessed suicidality retrospectively by adverse event reporting, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients. Of the patients included in the

³⁴ Rubin R et al. Acute psychotic reaction following ingestion of phentermine. Am J of Psychiatry 1964; 120: 1124-5

³⁵ Statistical review and evaluation: antiepileptic drugs and suicidality [23 May 2008] FDA Briefing Material <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-00-index.html> (Accessed 26 May 2010)

meta-analysis, the majority (27%) were taking topiramate. Of these topiramate-exposed patients, 72% were prescribed topiramate for an indication other than an underlying epileptic or psychiatric condition. Figure 14 depicts the estimated odds ratios and 95% confidence intervals for suicidal behavior or ideation by drug and all AEDs combined (overall). Topiramate reached nominal statistical significance with an odds ratio of 2.53 (95% CI 1.21, 5.85).

Figure 14: Suicidal behavior or ideation odds ratio estimates, placebo-controlled trials



Source: 10 July 2008 Joint Meeting of the Peripheral and Central Nervous Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee Statistical review Briefing Document Figure 2, Pg 24

• Metabolic acidosis

According to the TOPAMAX label, metabolic acidosis has been observed at doses as low as 50 mg/day of topiramate. The incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in adults in the epilepsy controlled clinical trial for topiramate monotherapy was 15% for the 50 mg/day dose. The incidence of markedly abnormal serum bicarbonate (absolute value <17 mEq/L and 5 mEq/L decrease from pretreatment) in the monotherapy trials was 1% for 50 mg/day. Consequences of untreated chronic metabolic acidosis may include hyperventilation, fatigue, anorexia, and increased risk for osteomalacia or osteoporosis.³⁶

• Nephrolithiasis

Topiramate is a carbonic anhydrase inhibitor and promotes renal stone formation by reducing urinary citrate excretion and increasing urinary pH.³⁷ According to the TOPAMAX label, a total of 32/2,086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development program reported the occurrence of kidney stones, an incidence about 2 to 4 times greater than expected in a similar, untreated population. In a double-blind monotherapy epilepsy

³⁶ Miraz N et al. Effect of topiramate on acid-base balance: extent, mechanism and effects. Br J Clin Pharmacol 2009; 68:655-61.

³⁷ Welch BJ et al. Biochemical and stone-risk profiles with topiramate treatment. Am J Kidney Dis 2006; 48:555-63.

study, a total of 4/319 (1.3%) of adults exposed to topiramate reported the occurrence of kidney stones.

- **Acute myopia and secondary angle closure glaucoma**

The TOPAMAX label states that a syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX. Symptoms typically occur within 1 month of initiating TOPAMAX therapy.

- **Pregnancy exposure**

There are five pregnancy categories (A, B, C, D, and X) used in current drug labeling. Fetal risk does not linearly increase from A to X. Categories C, D, and X are based not only on the risk observed from animal and/or human data but importantly on the potential benefit in pregnant women. TOPAMAX is currently labeled with the pregnancy category C designation which applies to drugs with positive teratogenic effects in animals, no adequate human studies, but with potential benefits to warrant the drug's use in pregnancy. A drug may also be classified as pregnancy category C if animal studies have not been conducted and there are no adequate and well controlled studies in pregnant women. Phentermine does not have animal data and limited human data have shown no increase in congenital malformations. A pregnancy category X applies to drugs with positive teratogenic effects in animal and human studies or post-marketing experience, and which offer no potential benefit when taken in pregnancy.

Animal studies

Topiramate was found to be teratogenic in several animal species. The TOPAMAX label lists fetal malformations related to bone growth and development in mouse (primarily craniofacial defects), rat (limb malformations including ectrodactyly, micromelia, and amelia), and rabbit (primarily rib and vertebral malformations). Fetal malformations occurred at clinically relevant doses for listed indications of epilepsy and migraine treatment, but sensitivity varied widely between mouse (most sensitive), rabbit (intermediate), and rat (least sensitive).

The teratogenic effect of topiramate alone in multiple animal species is directly relevant to risk assessment with PHEN/TPM. The maximum topiramate dose of PHEN/TPM (92 mg/day) is lower than the maximal daily dose approved for TOPAMAX (400 mg/day). Therefore, adjustment of exposure margins is necessary. Exposure margins are calculated by comparing the dose used in animals to the maximum recommended human dose (MRHD). This can be done by adjusting for body surface area (BSA) when plasma drug levels are unknown, but comparison of actual plasma drug levels (AUC) in animals and humans provides the most accurate estimate of exposure margin between nonclinical and clinical dose levels. Exposure margins in the TOPAMAX label are based on a BSA adjustment; however, there are now sufficient data to estimate total plasma drug exposure (AUC₀₋₂₄) in rats and rabbits, but not mice, for PHEN/TPM based on toxicity studies conducted by the applicant with the phentermine plus topiramate combination.

Table 29 summarizes the teratogenicity data for topiramate in animals with exposure margins adjusted for the maximum dose of topiramate in PHEN/TPM (92mg/day). Exposure margins, or 'human exposure multiples', were estimated based on body surface area and on estimated plasma

drug levels (AUC_{0-24}) for comparison. Note that using body surface area results in much higher human exposure multiples than those based on estimated AUC. The body surface area comparisons tend to over-estimate human exposure multiples for topiramate since, as noted, AUC multiples are considered the most accurate exposure comparisons. Based on an AUC comparison, topiramate is associated with teratogenicity in rabbits and rats at 6x and 34x the MRHD for PHEN/TPM. Plasma drug levels are not available in mice, so based on body surface area, topiramate was teratogenic at 2x the MRHD for PHEN/TPM (or essentially equivalent to clinical exposure). This represents a relatively wide range of sensitivity—2x to 34x the MRHD—across species, yet it is notable that teratogenicity occurs in all three species tested. It is difficult to extrapolate where humans fall along this spectrum of sensitivity.

Table 29 also includes data from embryofetal development studies with the phentermine plus topiramate combination in rats and rabbits, conducted by the applicant. The applicant chose a maximum dose of topiramate that is not associated with teratogenesis in either species. Indeed, the maximum doses of phentermine and topiramate tested provided drug exposure within 2-fold (and no higher) of the maximum human plasma exposure to high-dose PHEN/TPM. There were no drug-induced effects of combination phentermine plus topiramate treatment on embryofetal development or teratogenicity in either rats or rabbits. However, the embryofetal development studies were not designed to assess toxicity at teratogenic doses of topiramate. Rather, these studies were designed to investigate potential additive or synergistic effects on embryofetal development at a non-teratogenic dose of topiramate. The Division concluded that the combination of phentermine and topiramate at non-teratogenic doses did not result in teratogenesis, indicating a lack of significant drug interaction on this toxicity endpoint. These combination toxicity studies should be considered in the context of the known teratogenic profile of topiramate in multiple species, the wide range of sensitivity to teratogenesis across species, the data from human pregnancy registries, and the patient population intended for PHEN/TPM.

Table 29: Summary of topiramate teratogenicity

Summary of Topiramate Teratogenicity †			
Topiramate Treatment ^a	Teratogenic or Reprotoxic Finding	Human Exposure Multiple	
		Body Surface Area (mg/m ²)	AUC ₀₋₂₄ ^b
Rat			
25 mg/kg	None ^c	4x	2x
100 mg/kg	None	17x	8x
200 mg/kg	Offspring effects	35x	16x
400 mg/kg	Teratogenic	70x	34x
Rabbit			
25 mg/kg	None	9x	1x
35 mg/kg	Maternal/embryofetal death	12x	2x
120 mg/kg	Teratogenic	42x	6x
Mouse			
20 mg/kg	Teratogenic	2x	--

† Human exposure multiples based on maximum 15 mg PHEN/92 mg TPM dose in an obese population (100 kg; 6 / 34 mg/m², respectively) and clinical exposures of 2.5 / 80 µg*h/ml (respectively)

^a Topiramate alone or with phentermine to assess embryofetal (Seg 2) or pre- and post-natal (Seg 3) development

^b Actual or estimated (based on dose-proportional exposure)

^c Comparable treatment (30 mg/kg) caused persistent reductions in offspring body weight gain

Human experience with topiramate during pregnancy

The TOPAMAX label contains contact information for the North American Antiepileptic Drug Pregnancy Registry which has been established to collect information and provide scientific knowledge about safety and outcomes associated with pregnant women treated with anticonvulsant drugs. Several other registries have been established to track pregnancies exposed to anticonvulsant drugs including the UK Epilepsy and Pregnancy Registry. The FDA also has an Adverse Event Reporting System (AERS) which receives voluntary reporting of adverse events. The AERS database system is limited in attempting to determine a causal relationship since there is no control group and AERS data cannot be used to calculate the incidence of an adverse event in the United States; however, the AERS database was mined for adverse events reported with phentermine and topiramate exposed pregnancies. Available information, both published and unpublished, regarding topiramate exposure in pregnancy are described below.

- North American Antiepileptic Pregnancy Registry

In 2009, the North American Antiepileptic Pregnancy Registry released preliminary findings on the effects of monotherapy with six antiepileptic drugs including topiramate as well as the previously released data on lamotrigine and carbamazepine (Table 30).³⁸

Table 30: Antiepileptic drugs and prevalence of malformations

Compound Name	Brand Name	Total Malformations	Enrolled Pregnancies	Prevalence of Malformations	95% Confidence Intervals
phenytoin	Dilantin®	10	390	2.6 %	1.2 - 4.5 %
clonazepam	Klonopin®	2	50	4.0 %	0.68 - 12.6 %
gabapentin	Neurontin®	1	127	0.8 %	0.039 - 3.8 %
topiramate	Topamax®	8	197	4.1 %	1.9 - 7.6 %
oxcarbazepine	Trileptal®	2	121	1.7 %	0.28 - 5.4 %
levetiracetam	Keppra®	4	197	2.0 %	0.65 - 4.8 %
lamotrigine ¹	Lamictal®	16	684	2.3 %	1.3 - 3.8 %
carbamazepine ²	Tegretol®	22	873	2.6 %	1.5 - 4.3 %
external controls ³	n/a	1,119	69,277	1.6%	1.5 - 1.7 %

Source: www.aedpregnancyregistry.org Winter 2009 newsletter

The findings in the topiramate-exposed pregnancies showed a statistically significant increased rate (4.1%) across all malformations. The Registry's authors cautioned that the malformations were eight separate, common birth defects that did not show an increase for any specific abnormality. Topiramate dosing information was not provided with this report.

- UK Epilepsy and Pregnancy Registry

The UK Epilepsy and Pregnancy Registry published findings in topiramate-exposed pregnancies.³⁹ Of 70 topiramate monotherapy exposed pregnancies, the major congenital malformation rate was calculated as 4.8% (95% CI 1.7% to 13.3%). The three malformations reported were two oral cleft abnormalities, and one hypospadias (Table 31).

³⁸ <http://www.aedpregnancyregistry.org/> Winter 2009 newsletter [Accessed 31 May 2010]

³⁹ Hunt et al. Topiramate in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2008;71:272-6.

Table 31: Major congenital malformations with topiramate monotherapy

Table 2 Major congenital malformations with topiramate monotherapy									
No.	Dose TPM during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Major congenital malformation
1	200	29	G3P2	Partial	NR	41	3,850	F	Cleft lip and bilateral cleft palate
2	400	34	G3P2	NR	No	37	2,355	M	Hypospadias
3	600	27	G1P1	NR	Yes	39	3,289	NR	Cleft lip and palate

Source: Hunt et al. Neuro 2008

- FDA Adverse Event Reporting System

A total of 115 spontaneous reports of adverse fetal, neonatal, and/or postnatal events associated with administration of topiramate monotherapy in pregnancy were retrieved from the AERS database. The cases were reviewed by a FDA teratologist. The conclusions of the report are summarized here. Please refer to the complete report for detailed information. Seventy-six case reports were included in the final review after excluding duplicate or irrelevant reports. Over 80% of the reports were submitted from health professionals. Of the reports that included information on the treatment indication, the majority (47/51, 92%) of topiramate use was indicated for prevention of seizures. Four cases had an indication for migraine prevention. Four of the 76 cases were on concomitant medication including carbamazepine, lamotrigine, and chemotherapy/radiation therapy. The topiramate dose was reported in 45 of 76 cases and in the majority of these the topiramate dose was less than or equal to 200 mg/day (in 64% of cases). When timing of exposure was reported (42 reports), the majority of the topiramate exposure (37/42, 88%) occurred within the first trimester of gestation. Half of the 42 pregnancies did not continue exposure to topiramate beyond the first trimester. Of the 76 cases, five were excluded due to postnatal events, and four were excluded for genetic syndromes. The breakdown of congenital malformations reported for the remaining 67 cases are listed in Table 32.

Table 32: Congenital malformations' spectrum and reporting frequency

Type of malformation	N reported (percent of all malformation cases)*
Total reported malformation cases	67 (excluding congenital genetic syndromes)
- Malformations not specified	3
- Malformations specified	64
Craniofacial	21 /64 (32.8%)
- Cleft lip and/or palate	11
- Facial dysmorphism (incl. auricular dysplasia)	6
- Micrognathia	4

- Skull deformation and ossification abnormalities	3
- Macroglossia	1
Skeletal	19 /64 (29.9%)
- Limb malformations	16
Phalangeal (brachydactyly, adactyly, syndactyly)	8
Long bones (radius, femur hypoplasia, deformity)	5
Hip dysplasia, Talipes	6
Vertebral	4
Cardiovascular	15 /64 (23.4%)
- Ventricular or atrial septal defect	11
- Single ventricle	1
- Patent ductus arteriosus	1
- Pulmonary artery stenosis	1
- Aortic hypoplasia	1
- Aortic valve bicuspid	1
- Transposition of great arteries	1
Genito-urinary	9/ 64 (14.1%)
- Hypospadias	4
- Labia pudenda adhesions	2
- Ureteral malformation (double ureter)	1
- Hydronephrosis	1
- Nephrolithiasis	1
CNS	8/ 64 (12.5%)
- Spina bifida	3
- Microcephaly	1
- Hydrocephaly	1
- Microgyria	1
- Corpus callosum aplasia	1
- Syringomyelia	1
Gastro-intestinal	3/ 64 (4.7%)
- Hernia (diaphragmatic, umbilical, inguinal)	3
Neoplasia (hemangioma, glioma)	2 /64 (3.2 %)
Pulmonary	1/ 64 (1.6%)

*Individual percent values add to more than 100% because of multiple malformation cases

The reported malformations displayed a distinctive and consistent pattern. Dominating among the reported congenital birth defects were craniofacial malformations (predominantly oral clefts, but also facial and skull dysmorphism, micrognathia), as well as skeletal limb defects (long bone and phalangeal hypoplasia, aplasia or deformities, including adactyly, brachydactyly, syndactyly, radius or femoral hypoplasia, hip dysplasia, talipes). Both craniofacial and skeletal limb malformations were each reported in about 30% of the reviewed 64 malformation reports.

Confounding factors include concomitant drug use which was reported in four cases: two involving carbamazepine (first trimester), one – lamotrigine prior to pregnancy, and one– chemo- and radiation therapy 2 months before conception. The types of malformations reported in these cases (i.e., hemangioma and diaphragmatic hernia in the 2 carbamazepine cases; a single heart ventricle in the lamotrigine case) were different from the malformation pattern seen with topiramate alone. The genetic malformation syndrome Cri du chat was present in the pre-pregnancy chemo- and radiation exposure and was not included in Table 32. The adverse events reported at daily doses of 200 mg or less were not different by type and reporting frequency from those at daily doses of over 200 or over 400 mg. However, the small number of cases treated with doses greater than 400 mg/day (n=7) do not allow a definitive conclusion.

The malformation pattern of the AERS data is similar to the types of malformations seen in both the UK Epilepsy and Pregnancy Registry and topiramate developmental toxicity studies in experimental animal species and suggests that the reported malformations in topiramate-exposed pregnancy are related to topiramate exposure.

It has been suggested that infants of mothers with epilepsy are at greater risk for abnormalities because of their mother's underlying condition independent of anticonvulsant use. A study published in 2001 evaluated infants for major malformations, growth retardation, and midface and finger hypoplasia. Infants were categorized into three groups: 1) exposed to anticonvulsants in utero + mother with seizure disorder, 2) unexposed to anticonvulsants in utero + mother with seizure disorder, and 3) unexposed to anticonvulsants with no maternal history of seizures.⁴⁰ The incidence of congenital malformations was highest in group 1, while the infants from groups 2 and 3 had similar rates of malformations. Although these analyses were adjusted for maternal cigarette smoking, ingestion of alcohol, substance abuse, and severity of seizures, confounding by indication cannot be ruled out as a factor contributing to the results.

PHEN/TPM Safety

The integrated summary of safety (ISS) for PHEN/TPM is composed of the three pivotal Phase 3 trials and two supportive Phase 2 trials. The trials were divided into two cohorts based on duration of 6 months and 1 year. The cohorts are not mutually exclusive; therefore some individuals in studies OB-202, OB-302, and OB-303 count in both the 6-month and 1-year cohorts. Because individuals are included in both cohorts and review of the 6-month and 1-year data did not present distinctly different results, the briefing document focuses on the 1-year safety cohort for PHEN/TPM. The 1-year cohort consists of all randomized individuals from studies OB-302 and OB-303 and all individuals who entered study DM-230, the 6-month extension to study OB-202. Data were combined from OB-202 and DM-230 to provide 1-year safety data for these individuals. It is this reviewer's opinion that pooling of these studies is appropriate, as all study individuals were overweight or obese and represent the target population. There was also consistent drug titration regimens and uniform safety data collection across individual studies.

Table 33: Studies comprising the 1-year safety cohort for PHEN/TPM

⁴⁰ Holmes LB et al. The teratogenicity of anticonvulsant drugs. NEJM 2001;344:1132-8.

Study	Treatment groups	N	Age (years)	Population	Duration	Primary endpoint <u>Secondary/other endpoints</u>
OB-202/DM-230	<ul style="list-style-type: none"> Placebo Phentermine 15 mg and Topiramate 100 mg (during OB-202) PHEN/TPM 15/92 (during DM-230) 	55 75	Adults ≤ 70	BMI ≥ 27 kg/m ² and ≤ 45 kg/m ² with type 2 diabetes	56 weeks [OB-202 (28 weeks) + DM-230 (28 weeks)]	<ul style="list-style-type: none"> Change from baseline in HbA1c <u>Secondary</u> <ul style="list-style-type: none"> Absolute and % weight loss Δ in BMI Δ in waist circumference % with 5%, 10% weight loss Δ in HbA1c and insulin sensitivity (OGTT) Proportion of individuals achieving HbA1c levels $< 7\%$ and $< 6.5\%$ Δ in medications for CV/ metabolic Δ in lipid, BP, liver enzymes, Framingham risk score, urinary microalbumin Δ in IWQOL-Lite and VAS assessments Δ in apo A, apoB-100, VLDL, Lp(a), LDL particle size, hsCRP, C-peptide, fibrinogen, PAI-1, ICAM, VCAM
OB-302	<ul style="list-style-type: none"> Placebo PHEN/TPM 3.75/23 mg PHEN/TPM 15/92 mg 	514 241 512	Adults ≤ 70	BMI ≥ 35 kg/m ² Type 2 diabetes excluded	56 weeks	<ul style="list-style-type: none"> Weight loss at 56 weeks <u>Secondary</u> <ul style="list-style-type: none"> Absolute weight loss % with 10% weight loss Δ in waist circumference <u>Other</u> Δ in BMI, BP, lipids, fasting glucose, Framingham risk score, fat and lean body mass

Study	Treatment groups	N	Age (years)	Population	Duration	Primary endpoint <u>Secondary/other endpoints</u>
						by DEXA, hunger and satiety, IWQOL-Lite score, % with 15% weight loss
OB-303	<ul style="list-style-type: none"> Placebo PHEN/TPM 7.5/46 mg PHEN/TPM 15/92 mg 	994 498 995	Adults ≤ 70	BMI ≥ 27 kg/m ² and ≤ 45 kg/m ² Two or more weight-related comorbidities	56 weeks	Weight loss at 56 weeks <u>Secondary</u> <ul style="list-style-type: none"> Absolute weight loss % with 10% weight loss Δ in waist circumference <u>Other</u> Δ in BMI, BP, lipids, fasting serum glucose, HbA1c, insulin, glucose and insulin by OGTT, Framingham risk score, hunger and satiety, IWQOL-Lite score, fat and lean body mass by DEXA, insulin resistance parameters, SF-36 scores, % with 15% weight loss

Exposure to study drug

According to the FDA's 2007 draft Weight Management Guidance, a reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 individuals are randomized to active doses of the investigational product and no fewer than 1,500 individuals are randomized to placebo for 1 year of treatment. The 1-year cohort included a total of 2,321 individuals randomized to PHEN/TPM and 1,563 randomized to placebo. The safety set for the 1-year cohort which is defined as any randomized subject who received at least one dose of study medication, included 2,318 exposed to active drug and 1,561 exposed to placebo. Although lower than recommended in the guidance document, the Division agreed that the extent of exposure within the PHEN/TPM development program was adequate because of previous experience with the currently approved phentermine and topiramate products.

The overall extent of exposure to study drug in the 1-year cohort before adjustment for drug holidays or dose modifications was a mean of 286.1 days and a median of 391.0 days (Table 34). In total, 2373 (61.2%) individuals in the 1-year cohort had >52 weeks exposure. Exposure to study drug adjusting for drug holidays was similar to unadjusted.

Table 34: Extent of exposure to study drug – 1-year cohort (safety set)

Extent of exposure to study drug – 1-year cohort (safety set)						
1-year cohort						
	Placebo N=1561	PHEN/TPM 3.75/23 N=240	PHEN/TPM 7.5/46 N=498	PHEN/TPM 15/92 N=1580	PHEN/TPM Total N=2318	Total N=3879
Mean (SD), days	268.8 (152.82)	282.2 (148.36)	308.2 (142.35)	296.8 (147.52)	297.7 (146.62)	286.1 (149.80)
Median, days	389.0	391.0	392.0	392.0	392.0	391.0
>52 weeks ≤56 weeks, n (%)	398 (25.5)	55 (22.9)	167 (33.5)	458 (29.0)	680 (29.3)	1078 (27.8)
>56 weeks	464 (29.7)	88 (36.7)	180 (36.1)	563 (35.6)	831 (35.8)	1295 (33.4)
Applicant's Tables 24, Pg 87 ISS Data from studies OB-202/DM-230, OB-302, OB-303						

Dose modifications

Overall, the majority of individuals (60.4%) in the 1-year cohort completed the study on their original randomized treatment. However, a higher percentage of PHEN/TPM-treated individuals compared to placebo-treated individuals completed the study on the original randomized treatment regimen (Table 35). A higher percentage of individuals on the high-dose PHEN/TPM had a change in study medication dosing compared to the other treatment groups. There were three reasons available to investigators to explain a dose change: Drug tolerability, Event not related to drug, and Other. The applicant was asked to submit the verbatim reasons for the Other category. This information revealed that many of the Other reasons were related to adverse events, some of which were possibly or probably related to study drug.

Table 35: Summary of Dose Modifications: 1-year cohort (safety set)

1-year cohort (Safety set)					
	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=3879 n (%)
Completed study on randomized treatment	857 (54.9)	138 (57.5)	344 (69.1)	1003 (63.5)	1485 (64.1)
Any change to study medication dosing	216 (13.8)	33 (13.8)	102 (20.5)	352 (22.3)	487 (21.0)
Drug holiday	137 (8.8)	21 (8.8)	57 (11.4)	187 (11.8)	265 (11.4)
Drug Tolerability	20 (1.3)	7 (2.9)	16 (3.2)	74 (4.7)	97 (4.2)
Event not related to drug	49 (3.1)	7 (2.9)	18 (3.6)	50 (3.2)	75 (3.2)
Other	74 (4.7)	8 (3.3)	27 (5.4)	83 (5.3)	118 (5.1)
Drug reduction	55 (3.5)	11 (4.6)	50 (10.0)	219 (13.9)	280 (12.1)
Drug tolerability	30 (1.9)	7 (2.9)	31 (6.2)	164 (10.4)	202 (8.7)
Event not related to drug	4 (0.3)	0	1 (0.2)	8 (0.5)	9 (0.4)
Other	22 (1.4)	5 (2.1)	20 (4.0)	56 (3.5)	81 (3.5)
Uptitration after dose reduction	7 (0.4)	0	9 (1.8)	50 (3.2)	59 (2.5)
No uptitration	48 (3.1)	11 (4.6)	41 (8.2)	169 (10.7)	221 (9.5)
Switch to QOD dosing	39 (2.5)	7 (2.9)	37 (7.4)	143 (9.1)	187 (8.1)
Drug tolerability	19 (1.2)	4 (1.7)	22 (4.4)	105 (6.6)	131 (5.7)
Event not related to drug	5 (0.3)	0	1 (0.2)	5 (0.3)	6 (0.3)
Other	15 (1.0)	3 (1.3)	14 (2.8)	40 (2.5)	57 (2.5)
Return to daily dosing after switch to QOD dosing	27 (1.7)	4 (1.7)	25 (5.0)	96 (6.1)	125 (5.4)
Remaining on QOD dosing	12 (0.8)	3 (1.3)	12 (2.4)	47 (3.0)	62 (2.7)
Includes data from studies OB-202/DM-230, OB-301, OB-302, and OB-303 Source: ISS Table 26, Pg 91, Table 20 Submission 6 response to IR					

Overall Adverse Events

Adverse events (AEs) were defined as any untoward medical occurrence in individuals administered the trial treatment, whether or not they had a causal relationship to the treatment. The severity of the AE was assessed as mild, moderate, or severe:

- Mild: Does not interfere with the subject's usual function;
- Moderate: Interferes to some extent with the subject's usual function;
- Severe: Interferes significantly with the subject's usual function

For an adverse event to qualify as a serious adverse event (SAE), it had to meet one of the following criteria:

- Results in death
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect

In addition, adverse events that in the investigator's judgment significantly jeopardize individuals or require medical or surgical intervention in order to prevent any of the outcomes listed above were to be reported as a SAE.

Treatment-emergent adverse events 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.

Table 36 presents the overall adverse events. There was only one death and this was in a placebo-treated subject. The occurrence of serious adverse events (SAEs) was low and similar between the treatment groups. There was a higher proportion of PHEN/TPM-treated individuals who discontinued study drug treatment due to an adverse event compared to placebo-treated individuals. The majority of individuals experienced a TEAE with a higher proportion occurring in the PHEN/TPM exposed group.

Table 36: Overview of adverse events during the double-blind treatment period – 1-year cohort (safety set)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=3879 n (%)
Deaths	1 (0.1)	0	0	0	0
Any SAE	55 (3.5)	6 (2.5)	15 (3.0)	67 (4.2)	88 (3.8)
Treatment-emergent SAE	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)	77 (3.3)
Study drug discontinuations due to adverse events					
Any adverse event	132 (8.5)	28 (11.7)	58 (11.6)	276 (17.5)	362 (15.6)
Any TEAE	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)	359 (15.5)
Any SAE	15 (1.0)	2 (0.8)	4 (0.8)	18 (1.1)	24 (1.0)
Treatment emergent adverse events	1186 (76.0)	192 (80.0)	424 (85.1)	1377 (87.2)	1993 (86.0)
Source: Applicant's Table 28, Pg 95, ISS					

Deaths and Serious Adverse events

Deaths

There were no deaths reported in the Phase 1 program, which included 549 healthy individuals and 57 individuals with mild to severe renal or hepatic impairment.

There were no deaths reported in the Phase 2 program, which included 490 individuals.

One death, in a placebo-treated individual, occurred in the Phase 3 program. Subject OB 303/143-037 died from cardio-respiratory arrest. He was a 44-year-old Caucasian man with a history of hypertension, gastroesophageal reflux disease, and anxiety disorder randomized to placebo treatment. On Study Day 56, he was found unresponsive. Emergency medical services found him apneic and pulseless. He was admitted to hospital after resuscitative efforts restored a cardiac rhythm. Urine drug screen was positive for cocaine. One day after admission, cardiac enzymes were elevated. He never regained consciousness and expired two days after initial event. Additional diagnoses at the time of death included substance abuse and anoxic/toxic metabolic encephalopathy.

Non-fatal serious adverse events

In the evaluation of non-fatal SAEs in the first year of treatment, the overall incidence was similar among treatment groups (placebo 3.3%, low-dose PHEN/TPM 2.5%, mid-dose PHEN/TPM 2.8%, high-dose PHEN/TPM 3.6%).

There were four myocardial infarctions in the PHEN/TPM group and none in the placebo group. Three occurred within the first 6 months of treatment; the mean age was approximately 62 years; all were Caucasian; two were female; and three were past or current smokers. The narratives of these individuals are located in Appendix B. Although there were no documented MIs in the placebo group, the overall incidence of SAEs in the system organ class Cardiac Disorders was similar between placebo and active treatment (placebo 8/1561 0.5%, any PHEN/TPM 8/2318 0.3%).

There were three reports of deep vein thrombosis (DVT) in the PHEN/TPM-treated group compared to none in the placebo group. Two occurred in young women within the first 6 months of treatment. One of the women was pregnant and another was on oral contraceptives. The third case occurred in a 58-year-old man with a history of DVT. The narratives of these individuals are located in Appendix C.

Over the first year of treatment the proportion of gallbladder-related conditions was similar between the placebo (5/1561 0.3%) versus PHEN/TPM (8/2318 0.3%) treatment groups. Seven of the eight individuals in the PHEN/TPM groups who experienced a gallbladder complication were treated with high-dose PHEN/TPM.

There were two reports of nephrolithiasis and one of urinary calculus in the high-dose PHEN/TPM group and none in the placebo group. Topiramate is associated with kidney stone

formation which may be related to its inhibition of carbonic anhydrase which reduces urinary citrate excretion and increases urinary pH.

There were two individuals who experienced a cerebral ischemic event in the 1-year cohort, one in the placebo group and 1 in the high-dose PHEN/TPM group (acute non-hemorrhagic infarct). An additional placebo-treated subject (OB-202/0633) not included in the 1-year cohort experienced a thalamic infarction.

There was only one psychiatric SAE reported of bipolar disorder in a 68-year-old Caucasian female with a history of bipolar disorder on Zoloft for depression. Her medical history included past history of bipolar illness, positive suicidal ideas in the 1970s, and previous psychiatric hospitalizations. The study drug was permanently discontinued on Study Day 170 due to investigator's decision. On Study Day 178, she was seen in the physician's office for behavioral changes including confusion. On Study Day 192, she was experiencing delusions and a decreased ability to perform activities of daily living. On Study Day 203, she experienced symptoms of mania, delusions, and confusion. Treatment of the event included ziprasidone and aripiprazole. Recovery from these events occurred on Study Day 217 after stopping ziprasidone and starting sertraline HCl.

Table 37: Number and incidence of non-fatal treatment-emergent SAE: – 1-year cohort (safety set)

Number and incidence of non-fatal treatment-emergent SAE					
Integrated Summary Safety set-1 year cohort					
SOC Preferred term	Placebo N=1561 n(%)	PHEN/TPM 3.75/23 N=240 n(%)	PHEN/TPM 7.5/46 N=498 n(%)	PHEN/TPM 15/92 N=1580 n(%)	PHEN/TPM Total N=2318 n(%)
Total	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)	77 (3.3)
Infections and Infestations	2 (0.1)	2 (0.8)	3 (0.6)	11 (0.7)	16 (0.7)
Cellulitis	0	1 (0.4)	0	3 (0.2)	4 (0.2)
Appendicitis	0	1 (0.4)	0	3 (0.2)	3 (0.1)
Diverticulitis	1 (0.1)	0	2 (0.4)	0	2 (0.1)
Abdominal wall abscess	0	0	0	1 (0.1)	1 (0.04)
Bursitis infective	0	0	1 (0.2)	0	1 (0.04)
Clostridial infection	0	0	0	1 (0.1)	1 (0.04)
Gastroenteritis	1 (0.1)	0	0	0	0
Lobar pneumonia	0	0	0	1 (0.1)	1 (0.04)
Pneumonia	0	0	0	1 (0.1)	1 (0.04)
Staphylococcal infection	0	0	0	1 (0.1)	1 (0.04)
Viral infection	0	0	0	1 (0.1)	1 (0.04)
Cardiac disorders	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)	8 (0.3)
Coronary artery disease	4 (0.3)	0	0	0	0
Myocardial infarction	0	1 (0.4)	1 (0.2)	2 (0.1)	4 (0.2)
Atrial fibrillation	1 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.1)
Angina pectoris	1 (0.1)	0	0	1 (0.1)	1 (0.04)
Acute coronary syndrome	0	0	0	1 (0.1)	1 (0.04)

Number and incidence of non-fatal treatment-emergent SAE					
Integrated Summary Safety set-1 year cohort					
SOC Preferred term	Placebo N=1561 n(%)	PHEN/TPM 3.75/23 N=240 n(%)	PHEN/TPM 7.5/46 N=498 n(%)	PHEN/TPM 15/92 N=1580 n(%)	PHEN/TPM Total N=2318 n(%)
Myocardial ischemia	1 (0.1)	0	0	0	0
Tachycardia	0	0	1 (0.2)	0	1 (0.04)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (0.5)	0	1 (0.2)	6 (0.4)	7 (0.3)
Breast cancer	1 (0.1)	0	0	3 (0.2)	3 (0.1)
Prostate cancer	4 (0.3)	0	0	0	0
Lung neoplasm malignant	1 (0.1)	0	0	1 (0.1)	1 (0.04)
Breast cancer metastatic	1 (0.1)	0	0	0	0
Metastatic neoplasm	0	0	0	1 (0.1)	1 (0.04)
Myeloid leukemia	0	0	0	1 (0.1)	1 (0.04)
Rectal cancer	1 (0.1)	0	0	0	0
Uterine leiomyoma	0	0	1 (0.2)	0	1 (0.04)
Hepatobiliary disorders	5 (0.3)	1 (0.4)	0	7 (0.4)	8 (0.3)
Cholelithiasis	5 (0.3)	1 (0.4)	0	3 (0.2)	4 (0.2)
Cholecystitis acute	0	0	0	2 (0.1)	2 (0.1)
Bile duct stone	0	0	0	1 (0.1)	1 (0.04)
Cholangitis	1 (0.1)	0	0	0	0
Cholecystitis	0	0	0	1(0.1)	1 (0.04)
Musculoskeletal and connective tissue disease	4 (0.3)	0	0	6 (0.4)	6 (0.3)
Intervertebral disc protrusion	1 (0.1)	0	0	1 (0.1)	1 (0.04)
Arthralgia	1 (0.1)	0	0	0	0
Cervical spine stenosis	0	0	0	1 (0.1)	1 (0.04)
Costochondritis	0	0	0	1 (0.1)	1 (0.04)
Gouty arthritis	1 (0.1)	0	0	0	0
Intervertebral disc degeneration	0	0	0	1 (0.1)	1 (0.04)
Lumbar spinal stenosis	0	0	0	1 (0.1)	1 (0.04)
Musculoskeletal chest pain	0	0	0	1 (0.1)	1 (0.04)
Spinal osteoarthritis	1 (0.1)	0	0	0	0
Vascular disorders	2 (0.1)	2 (0.8)	1 (0.2)	4 (0.3)	7 (0.3)
Deep vein thrombosis	0	1 (0.4)	0	2 (0.1)	3 (0.1)
Hypertension	2 (0.1)	0	0	1 (0.1)	1 (0.04)
Hypotension	0	0	1 (0.2)	1 (0.1)	2 (0.1)
Thrombophlebitis superficial	0	1 (0.4)	0	0	1 (0.04)

Number and incidence of non-fatal treatment-emergent SAE					
Integrated Summary Safety set-1 year cohort					
SOC Preferred term	Placebo N=1561 n(%)	PHEN/TPM 3.75/23 N=240 n(%)	PHEN/TPM 7.5/46 N=498 n(%)	PHEN/TPM 15/92 N=1580 n(%)	PHEN/TPM Total N=2318 n(%)
Gastrointestinal disorders	5 (0.3)	0	0	3 (0.2)	3 (0.1)
Colitis ischemic	1 (0.1)	0	0	0	0
Gastric ulcer	1 (0.1)	0	0	0	0
Gastric ulcer hemorrhage	0	0	0	1 (0.1)	1 (0.04)
Gastroesophageal reflux disease	0	0	0	1 (0.1)	1 (0.04)
Intestinal obstruction	1 (0.1)	0	0	0	0
Esophageal spasm	0	0	0	1 (0.1)	1 (0.04)
Pancreatitis	1 (0.1)	0	0	0	0
Small intestinal obstruction	1 (0.1)	0	0	0	0
General disorders and administration site conditions	7 (0.4)	0	0	1 (0.1)	1 (0.04)
Chest pain	4 (0.3)	0	0	1 (0.1)	1 (0.04)
Non-cardiac chest pain	2 (0.1)	0	0	0	0
Catheter related complication	1 (0.1)	0	0	0	0
Nervous system disorders	4 (0.3)	0	2 (0.4)	2 (0.1)	4 (0.2)
Syncope	2 (0.1)	0	0	1 (0.1)	1 (0.04)
Brain mass	0	0	1 (0.1)	0	1 (0.04)
Brain stem infarction	1	0	0	0	0
Cerebral infarction	0	0	0	1 (0.1)	1 (0.04)
Dizziness	0	0	1 (0.2)	0	1 (0.04)
Headache	1 (0.1)	0	0	0	0
Transient ischemic attack	1 (0.1)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (0.2)	0	2 (0.4)	2 (0.1)	4 (0.2)
Pulmonary embolism	2 (0.1)	0	0	2 (0.1)	2 (0.1)
Asthma	1 (0.1)	0	2 (0.4)	0	2 (0.1)
Reproductive system and breast disorders	3 (0.2)	0	0	3 (0.2)	3 (0.1)
Coital bleeding	0	0	0	1 (0.1)	1 (0.04)
Ovarian cyst ruptured	0	0	0	1 (0.1)	1 (0.04)
Pelvic pain	1 (0.1)	0	0	0	0
Uterine polyp	1 (0.1)	0	0	0	0
Uterine prolapse	1 (0.1)	0	0	0	0
Uterovaginal prolapse	0	0	0	1 (0.1)	1 (0.04)

Number and incidence of non-fatal treatment-emergent SAE					
Integrated Summary Safety set-1 year cohort					
SOC Preferred term	Placebo N=1561 n(%)	PHEN/TPM 3.75/23 N=240 n(%)	PHEN/TPM 7.5/46 N=498 n(%)	PHEN/TPM 15/92 N=1580 n(%)	PHEN/TPM Total N=2318 n(%)
Renal and urinary disorders	2 (0.1)	0	0	3 (0.2)	3 (0.1)
Nephrolithiasis	0	0	0	2 (0.1)	2 (0.1)
Calculus urinary	0	0	0	1 (0.1)	1 (0.04)
Hematuria	1 (0.1)	0	0	0	0
Renal failure acute	1 (0.1)	0	0	0	0
Injury, poisoning, and procedural complications	2 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.1)
Anemia postoperative	1 (0.1)	0	0	0	0
Hip fracture	0	0	1 (0.2)	0	1 (0.04)
Incisional hernia	0	0	0	1 (0.1)	1 (0.04)
Tibia fracture	1 (0.1)	0	0	0	0
Metabolism and nutrition disorders	2 (0.1)	0	0	2 (0.1)	2 (0.1)
Dehydration	0	0	0	1 (0.1)	1 (0.04)
Electrolyte imbalance	0	0	0	1 (0.1)	1 (0.04)
Hypokalemia	1 (0.1)	0	0	0	0
Hyponatremia	1 (0.1)	0	0	0	0
Ear and labyrinth disorders	0	0	1 (0.2)	1 (0.1)	2 (0.1)
Tinnitus	0	0	1 (0.2)	0	1 (0.04)
Vertigo	0	0	0	1 (0.1)	1 (0.04)
Skin and subcutaneous tissue disorders	1 (0.1)	0	0	1 (0.1)	1 (0.04)
Skin ulcer	0	0	0	1 (0.1)	1 (0.04)
Urticaria	1 (0.1)	0	0	0	0
Endocrine disorders	0	0	1 (0.2)	0	1 (0.04)
Goiter	0	0	1 (0.2)	0	1 (0.04)
Immune system disorders	0	0	0	1 (0.1)	1 (0.04)
Hypersensitivity	0	0	0	1 (0.1)	1 (0.04)
Investigations	0	0	0	1 (0.1)	1 (0.04)
Liver function test abnormal	0	0	0	1 (0.1)	1 (0.04)
Psychiatric disorders	0	0	0	1 (0.1)	1 (0.04)
Bipolar disorder	0	0	0	1 (0.1)	1 (0.04)
Source: Section 5.3.5.3.2 ISS Table 47, Pg 1340 Includes data from studies OB-202 and DM-230 (combined), OB-302, and OB-303					

Treatment-emergent adverse events

There was a higher incidence of TEAEs in the PHEN/TPM groups as compared to the placebo group in the 1-year cohort (Table 38). The organ system classifications with the most common TEAEs and largest differences between PHEN/TPM treated and placebo groups were nervous, gastrointestinal, and psychiatric systems. The Cardiac disorders SOC also demonstrated a higher incidence of TEAEs in the PHEN/TPM compared to the placebo group although the overall incidence was smaller than the previously mentioned organ systems.

Overall the most common TEAE was paresthesia, which was observed in approximately 20% of individuals treated with the highest dose of PHEN/TPM (15/92 mg) compared with approximately 2% in the placebo group. Many TEAEs appeared to show a clear or suggestive dose-response relationship. These TEAEs included: dry mouth, constipation, paresthesia, dysgeusia, dizziness, hypoaesthesia, disturbance in attention, irritability, insomnia, alopecia, cough, and hypokalemia. Although a clear dose response was not observed with the TEAE of palpitations, it bears noting that all treatment doses of PHEN/TPM exhibited a higher incidence of palpitations compared to placebo.

Table 38: Number and incidence of treatment-emergent adverse events by system organ class - 1-year cohorts (safety set)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Total	1186 (76.0)	192 (80.0)	424 (85.1)	1377 (87.2)	1993 (86.0)
Infections and Infestations	644 (41.3)	126 (52.5)	219 (44.0)	730 (46.2)	1075 (46.4)
Gastrointestinal disorders	394 (25.2)	73 (30.4)	195 (39.2)	724 (45.8)	992 (42.8)
Nervous system disorders	317 (20.3)	58 (24.2)	182 (36.5)	685 (43.4)	925 (39.9)
Musculoskeletal and connective tissue disorders	319 (20.4)	48 (20.0)	107 (21.5)	340 (21.5)	495 (21.4)
Psychiatric disorders	172 (11.0)	34 (14.2)	74 (14.9)	362 (22.9)	470 (20.3)
General disorders and administration site conditions	200 (12.8)	32 (13.3)	83 (16.7)	303 (19.2)	418 (18.0)
Eye disorders	163 (10.4)	32 (13.3)	72 (14.5)	236 (14.9)	340 (14.7)
Respiratory, thoracic and mediastinal disorders	193 (12.4)	33 (13.8)	64 (12.9)	254 (16.1)	351 (15.1)
Skin and subcutaneous tissue disorders	145 (9.3)	17 (7.1)	65 (13.1)	244 (15.4)	326 (14.1)
Injury, poisoning, and procedural complications	193 (12.4)	19 (7.9)	77 (15.5)	197 (12.5)	293 (12.6)
Metabolism and nutrition disorders	121 (7.8)	12 (5.0)	50 (10.0)	158 (10.0)	220 (9.5)
Investigations	108 (6.9)	16 (6.7)	40 (8.0)	139 (8.8)	195 (8.4)
Reproductive system and breast disorders	62 (4.0)	15 (6.3)	25 (5.0)	114 (7.2)	154 (6.6)
Vascular disorders	91 (5.8)	10 (4.2)	27 (5.4)	76 (4.8)	113 (4.9)
Renal and urinary disorders	39 (2.5)	9 (3.8)	10 (2.0)	82 (5.2)	101 (4.4)
Ear and labyrinth disorders	38 (2.4)	5 (2.1)	21 (4.2)	65 (4.1)	91 (3.9)
Cardiac disorders	28 (1.8)	4 (1.7)	19 (3.8)	56 (3.5)	79 (3.4)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Immune system disorders	45 (2.9)	5 (2.1)	10 (2.0)	31 (2.0)	46 (2.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	23 (1.5)	1 (0.4)	7 (1.4)	26 (1.6)	34 (1.5)
Hepatobiliary disorders	12 (0.8)	3 (1.3)	2 (0.4)	22 (1.4)	27 (1.2)
Endocrine disorders	12 (0.8)	1 (0.4)	4 (0.8)	13 (0.8)	18 (0.8)
Blood and lymphatic system disorders	19 (1.2)	2 (0.8)	6 (1.2)	24 (1.5)	32 (1.4)
Congenital, familial and genetic disorders	1 (0.1)	0	0	6 (0.4)	6 (0.3)
Social circumstances	0	0	1 (0.2)	6 (0.4)	7 (0.3)
Surgical and medical procedures	1 (0.1)	0	0	0	0

Source: Applicant's Post-text table 43, Pg 935 ISS

Table 39: Incidence of most common treatment emergent adverse events occurring in ≥2% of individuals and more frequently with PHEN/TPM than placebo in 1-year cohort (safety set)

Treatment emergent events observed in ≥2% of individuals and more frequently with PHEN/TPM than placebo in 1-year cohort				
	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)
Infections and Infestations				
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				
Dry mouth	43 (2.8)	16 (6.7)	67 (13.5)	301 (19.1)
Constipation	96 (6.1)	19 (7.9)	75 (15.1)	255 (16.1)
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)
Oral paresthesia	4 (0.3)	1 (0.4)	3 (0.6)	35 (2.2)
Nervous system disorders				
Paresthesia	30 (1.9)	10 (4.2)	68 (13.7)	315 (19.9)

Treatment emergent events observed in $\geq 2\%$ of individuals and more frequently with PHEN/TPM than placebo in 1-year cohort				
	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)
Headache	145 (9.3)	25 (10.4)	35 (7.0)	167 (10.6)
Dysgeusia	17 (1.1)	3 (1.3)	37 (7.4)	149 (9.4)
Dizziness	53 (3.4)	7 (2.9)	36 (7.2)	136 (8.6)
Hypoaesthesia	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				
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				
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)
General disorders				
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)
Thirst	11 (0.7)	5 (2.1)	9 (1.8)	31 (2.0)
Chest discomfort	7 (0.4)	5 (2.1)	1 (.2)	14 (0.9)
Respiratory, thoracic, and mediastinal disorders				
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)
Eye disorders				
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 pain				
Procedural pain	26 (1.7)	5 (2.1)	12 (2.4)	30 (1.9)
Joint sprain	23 (1.5)	0	10 (2.0)	16 (1.0)
Skin and subcutaneous tissue				
Alopecia	11 (0.7)	5 (2.1)	13 (2.6)	59 (3.7)
Rash	34 (2.2)	4 (1.7)	10 (2.0)	41 (2.6)

Treatment emergent events observed in $\geq 2\%$ of individuals and more frequently with PHEN/TPM than placebo in 1-year cohort				
	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)
Metabolism and nutrition				
Decreased appetite	10 (0.6)	5 (2.1)	9 (1.8)	23 (1.5)
Hypokalemia	6 (0.4)	1 (0.4)	7 (1.4)	40 (2.5)
Reproductive system and breast disorders				
Dysmenorrhea	3 (0.2)	5 (2.1)	2 (0.4)	13 (0.8)
Cardiac				
Palpitations	12 (0.8)	2 (0.8)	12 (2.4)	27 (1.7)
Source: Applicant Table 43, Pg 935 ISS				

Discontinuations

Table 40 lists the disposition of individuals in the 1-year cohort. There were two types of discontinuations. Individuals could (1) discontinue study drug but still remain in the study and attend follow-up visits or (2) withdraw all study participation. More individuals on PHEN/TPM completed all visits on study drug compared to placebo. As expected individuals in the PHEN/TPM-treatment groups discontinued less for lack of efficacy than placebo-treatment groups and PHEN/TPM-treatment groups had a higher incidence of discontinuations of study drug due to an adverse event than the placebo group.

Table 40: Subject disposition - Randomized set - 1-year cohort

	Placebo N=1563 n (%)	PHEN/TPM 3.75/23 N=241 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1582 n (%)	PHEN/TPM TOTAL N=2321 n (%)	TOTAL N=3884 n (%)
Randomized	1563 (100.0)	241 (100.0)	498 (100.0)	1582 (100.0)	2321 (100.0)	3884 (100.0)
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 non-compliance	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	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)
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)	659 (28.4)	1282 (33.0)

	Placebo N=1563 n (%)	PHEN/TPM 3.75/23 N=241 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1582 n (%)	PHEN/TPM TOTAL N=2321 n (%)	TOTAL N=3884 n (%)
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 non-compliance	14 (0.9)	4 (1.7)	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)
Safety set	1561 (99.9)	240 (99.6)	498 (100.0)	1580 (99.9)	2318 (99.9)	3879 (99.9)

Data from studies OB-202/DM-230, OB-302, and OB-303 are included.
Individuals may be counted in both discontinuation sections.
Source: Applicant's Table 22 ISS, Pg 82

Adverse events leading to discontinuation

Within the 1-year cohort, 490 (12.6%) individuals had a treatment-emergent adverse event which resulted in study drug discontinuation (SDAE). The incidence of SDAEs was suggestive of a dose-response relationship [placebo 8.4%, low-dose 11.3%, mid-dose 11.6%, high-dose 17.3%]. Table 41 lists all the SDAEs resulting in study drug discontinuation by system organ class. The system organ classifications with a 1.0% difference in frequency of events leading to discontinuation between the placebo and PHEN/TPM-treated groups were Nervous System Disorders (1.6% versus 4.5%), Psychiatric Disorders (1.2% versus 4.1%), and Gastrointestinal Disorders (0.8% versus 2.4%).

Table 42 lists the most frequently reported ($\geq 1\%$) SDAEs; all were related to Nervous or Psychiatric disorders. There were no SDAEs in the placebo group that occurred at an incidence of $\geq 1\%$. In the high-dose PHEN/TPM group, 21 individuals or 1.3% of individuals discontinued due to depression versus none in the other treatment groups.

Table 41: Number and frequency of individuals with SDAEs – 1-year cohort (safety set)

Number and Frequency of Individuals with TEAE leading to discontinuation of study medication: 1-year cohort (safety set)					
System Organ Class Preferred Term	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Total	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)	359 (15.5)
Nervous System Disorders	25 (1.6)	7 (2.9)	17 (3.4)	81 (5.1)	105 (4.5)
Psychiatric Disorders	19 (1.2)	6 (2.5)	12 (2.4)	76 (4.8)	94 (4.1)
Gastrointestinal disorders	13 (0.8)	2 (0.8)	12 (2.4)	42 (2.7)	56 (2.4)
General disorders and administration site conditions	18 (1.2)	5 (2.1)	6 (1.2)	36 (2.3)	47 (2.0)
Eye disorders	15 (1.0)	6 (2.5)	9 (1.8)	23 (1.5)	38 (1.6)
Skin and subcutaneous tissue disorders	9 (0.6)	0	3 (0.6)	16 (1.0)	19 (0.8)

Number and Frequency of Individuals with TEAE leading to discontinuation of study medication: 1-year cohort (safety set)					
System Organ Class Preferred Term	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Cardiac disorders	10 (0.6)	2 (0.8)	2 (0.4)	11 (0.7)	15 (0.6)
Renal and urinary disorders	4 (0.3)	1 (0.4)	1 (0.2)	18 (1.1)	20 (0.9)
Vascular disorders	7 (0.4)	1 (0.4)	4 (0.8)	10 (0.6)	15 (0.6)
Respiratory, thoracic, and mediastinal disorders	4 (0.3)	1 (0.4)	2 (0.4)	14 (0.9)	17 (0.7)
Investigations	8 (0.5)	0	2 (0.4)	8 (0.5)	10 (0.4)
Infections and infestations	4 (0.3)	2 (0.8)	2 (0.4)	8 (0.5)	12 (0.5)
Musculoskeletal and connective tissue disorders	5 (0.3)	0	2 (0.4)	8 (0.5)	10 (0.4)
Ear and labyrinth disorders	2 (0.1)	0	1 (0.2)	7 (0.4)	8 (0.3)
Neoplasms benign, malignant and unspecified	4 (0.3)	0	0	6 (0.4)	6 (0.3)
Metabolism and nutrition disorders	1 (0.1)	0	0	5 (0.3)	5 (0.2)
Reproductive system and breast disorders	1 (0.1)	0	1 (0.2)	3 (0.2)	4 (0.2)
Hepatobiliary disorders	1 (0.1)	0	1 (0.2)	2 (0.1)	3 (0.1)
Injury, poisoning, and procedural complications	0	0	0	2 (0.1)	2 (0.1)
Immune system disorders	0	0	0	1 (0.1)	1 (0.04)
Includes data from studies OB-202/DM-230, OB-302, OB-303					
Source: ISS Post-text Table 48, pg 1346					

Table 42: Number and frequency of individuals with SDAEs of $\geq 1\%$ - 1-year cohort (safety set)

Treatment group	Preferred term	n (%)
Placebo N=1561	None	0
PHEN/TPM 3.75/23 N=240	Blurred vision	5 (2.1)
	Headache	4 (1.7)
PHEN/TPM 7.5/46 N=498	Dizziness	6 (1.2)
	Paresthesia	5 (1.0)
PHEN/TPM 15/92 N=1580	Insomnia	25 (1.6)
	Depression	21 (1.3)
	Irritability	18 (1.1)
	Paresthesia	18 (1.1)
	Anxiety	17 (1.1)
Includes data from studies OB-202, DM-230, OB-302, and OB-303		
Source: ISS Table 48, Pg 1346		

Targeted medical events

The applicant and the Division agreed on several Targeted Medical Events (TME) (Table 43) to be analyzed separately based on the known side-effect profiles of phentermine and topiramate. The TMEs were specified at the preferred term level and categorized by subclass and class. The full listing of preferred terms is provided in Appendix A.

Table 43: Listing of Targeted Medical Events by Class and Subclass

Listing of Targeted Medical Events by Class and Subclass	
Targeted Medical Event Class	Targeted Medical Event Subclass
Cardiac Disorders	Cardiac Arrhythmia Ischemic Heart Disease
Cognitive Disorders	Attention Language Memory Impairment Other Cognitive Disorders NOS
Drug Abuse/Withdrawal	Drug Abuse Drug Withdrawal
Menstrual Disorders	Menstrual Disorders
Ophthalmic Disorders	Ophthalmic Disorders
Psychiatric Disorders	Anxiety Depression Sleep Disorders Suicide/Self Injury
Psychomotor Disorders	Psychomotor Disorders
Source: Applicant's Table 54, ISS Pg 198	

By TME class, the mid- and high-dose PHEN/TPM-treated groups had a higher frequency of adverse events compared to the placebo group aside from the Drug Abuse/Withdrawal class.

Table 44: Number (%) of individuals with treatment-emergent Targeted Medical Events by class and subclass – 1-year cohort (safety set)

Number of individuals with treatment-emergent adverse events categorized as TME by class and subclass: - 1-year cohort (safety set)					
TME Class TME Subclass	Placebo N=1561 N (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM TOTAL N=2318 n (%)
Psychiatric disorders class	161 (10.3)	38 (15.8)	72 (14.5)	325 (20.6)	435 (18.8)
Sleep disorders subclass	89 (5.7)	16 (6.7)	34 (6.8)	170 (10.8)	220 (9.5)
Anxiety subclass	41 (2.6)	11 (4.6)	24 (4.8)	125 (7.9)	160 (6.9)
Depression (SMQ) subclass ^[1]	53 (3.4)	12 (5.0)	19 (3.8)	121 (7.7)	152 (6.6)
Suicide/self-injury (SMQ) subclass	1 (0.1)	1 (0.4)	0	0	1 (0.04)
Cognitive disorders class	26 (1.7)	5 (2.0)	28 (5.6)	124 (7.8)	157 (6.8)
Attention subclass	10 (0.6)	1 (0.4)	10 (2.0)	56 (3.5)	67 (2.9)
Memory impairment subclass	10 (0.6)	2 (0.8)	9 (1.8)	40 (2.5)	51 (2.2)
Language subclass	1 (0.1)	0	3 (0.6)	19 (1.2)	22 (0.9)
Other cognitive disorders NOS Subclass ^[2]	8 (0.5)	2 (0.8)	8 (1.6)	33 (2.1)	43 (1.7)
Cardiac disorders class	36 (2.3)	4 (1.7)	24 (4.8)	78 (4.9)	106 (4.6)
Cardiac arrhythmia (SMQ) subclass	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)	98 (4.2)
Ischemic heart disease (SMQ) subclass	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)	8 (0.3)
Ophthalmic disorders class	27 (1.7)	6 (2.5)	12 (2.4)	39 (2.5)	57 (2.5)
Ophthalmic disorder subclass	27 (1.7)	6 (2.5)	12 (2.4)	39 (2.5)	57 (2.5)
Psychomotor disorders class	1 (0.1)	0	2 (0.4)	12 (0.8)	14 (0.6)
Psychomotor disorder subclass	1 (0.1)	0	2 (0.4)	12 (0.8)	14 (0.6)
Drug abuse/withdrawal class	0	0	0	0	0
Drug abuse (SMQ) subclass	0	0	0	0	0
Drug withdrawal (SMQ) subclass	0	0	0	0	0

Number of individuals with treatment-emergent adverse events categorized as TME by class and subclass: - 1-year cohort (safety set)					
TME Class	Placebo	PHEN/TPM	PHEN/TPM	PHEN/TPM	PHEN/TPM
TME Subclass	N=1561	3.75/23	7.5/46	15/92	TOTAL
	N (%)	N=240	N=498	N=1580	N=2318
		n (%)	n (%)	n (%)	n (%)
Source: Applicant's Table 31, Pg 105 ISS					
¹ 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					
² Revised with the addition of "Feeling Abnormal" TEAE within the Cognitive subclass Other Cognitive NOS					

Psychiatric disorders TME

The psychiatric disorders TME were divided into four subclasses: Sleep, Anxiety, Depression, and Suicide/self injury which are described below.

Sleep disorders subclass

PHEN/TPM-treated individuals were almost two times more likely to experience a sleep disorder than placebo-treated individuals. The incidence of sleep disorders suggested a dose-response relationship (placebo 5.7%, low dose 6.7%, mid-dose 6.8%, and high-dose 10.8%). The majority of the TEAEs occurring in the Sleep disorder subclass were related to insomnia and most were mild in severity. There were no serious TEAEs within this subclass. Of the individuals with a sleep disorder adverse event, approximately 13% of PHEN/TPM-treated individuals discontinued study drug due to the sleep disorder versus 8% of placebo-treated individuals.

Anxiety subclass

PHEN/TPM-treated individuals were approximately 2.5 times more likely to experience a TEAE related to anxiety compared to placebo-treated individuals. Within this subclass, a dose-response relationship was suggested for the preferred term of irritability (placebo 0.7%, low-dose 1.7%, mid-dose 2.6%, high-dose 3.7%). Overall, the majority of the events were mild in severity; however, severe anxiety related events occurred with a slightly higher frequency in the PHEN/TPM-treated group (13/160, 8.1%) compared to placebo (3/41, 7.3%). More PHEN/TPM-treated individuals experienced the first event within the first four weeks of treatment in contrast to placebo-treated individuals who experienced the first event after the titration period. PHEN/TPM-treated individuals who experienced an anxiety TME were almost twice as likely to discontinue the study drug versus placebo-treated individuals who experienced an anxiety TME.

Depression subclass

A higher frequency of individuals in the PHEN/TPM-treated group experienced a depression-related TEAE compared to the placebo-treated group. The majority of the events in the PHEN/TPM-treated group were mild in severity; however, a higher incidence of events rated as severe occurred in the PHEN/TPM-treated group (10/152; 6.6%) compared to the placebo-treated group (2/53, 3.8%). There were no serious adverse events within this targeted medical event. The preferred term within this subclass that occurred with the highest frequency was depression. The majority of individuals who had a depression TME experienced the first event after the first four weeks of treatment. Of the individuals with a depression-related TEAE, 23% of the PHEN/TPM-exposed and 7.5% of placebo-exposed discontinued the study drug due to this event. Individuals who discontinued due to a depression-related AE had on average a higher total PHQ-9 score (see below) than individuals who did not discontinue.

Suicide/self-injury subclass

There were a total of two events within the 1-year cohort. Within the entire clinical development program for PHEN/TPM there were three episodes of treatment emergent adverse events coded as suicidal ideation; one in a placebo-treated subject (OB-303/151-080) and two episodes in PHEN/TPM-treated individuals (OB-302/148-017, OB-

301/127-019). An additional subject, OB 302/196-035 presented with suicidal ideation and hallucinations 105 days after discontinuing drug for the TEAE of “feeling funny”. This subject is not included in the Suicide/Self-injury TME. The narratives for these individuals are presented in Appendix D.

Assessment of Depression (PHQ-9)

The Patient Health Questionnaire 9 (PHQ-9) depression scale is composed of nine items based on the nine criteria on which the diagnosis of DSM-IV depressive disorders is based (Figure 15). Major depression is diagnosed if five or more of the nine depressive symptom criteria have been present at least “more than half the days” in the past two weeks, and one of the symptoms is depressed mood or anhedonia. Major depression is also diagnosed if Question 9: “thoughts that you would be better off dead or of hurting yourself in some way” is checked. The total PHQ-9 score ranges from 0 to 27. Scores of 5, 10, 15, and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively (Table 45). Current recommendations suggest a score of 10 as a screening cut point for depression, which has a sensitivity for major depression of 88% and specificity of 88%.⁴¹

⁴¹ Kroenke, K, Spitzer R. The PHQ-9: A new depression diagnostic and severity measure. *Psychiatric Annals* 2002; 32: 1-7.

Figure 15: Patient Health Questionnaire (PHQ-9)

Nine Symptom Checklist				
Over the <u>last 2 weeks</u> , how often have you been bothered by any of the following problems?				
	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things.....	0	1	2	3
2. Feeling down, depressed, or hopeless.....	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much.....	0	1	2	3
4. Feeling tired or having little energy.....	0	1	2	3
5. Poor appetite or overeating.....	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down.....	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.....	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.....	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way.....	0	1	2	3
(For office coding: Total Score ____ = ____ + ____ + ____)				
If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?				
Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<small>From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research information, contact Dr. Spitzer at rls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission.</small>				

Table 45: PHQ-9 Scoring scale

PHQ-9 Scoring scale	
PHQ-9 Score	Depression Severity
0 to 4	None
5 to 9	Mild
10 to 14	Moderate
15 to 19	Moderately Severe
20 to 27	Severe

For the 1-year safety cohort at baseline, the majority of individuals had no clinical depression by PHQ-9 score (Table 46).

Table 46: PHQ-9 Depression severity at baseline ISS 1-year cohort (safety set)

ISS one-year cohort: PHQ-9 Depression severity at Baseline				
	Placebo n (%) N=1561	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)
None	1151 (73.7)	185 (77.1)	379 (76.1)	1172 (74.2)
Mild	338 (21.7)	47 (19.6)	92 (18.5)	345 (21.8)
Moderate	10 (0.6)	1 (0.4)	4 (0.8)	11 (0.7)
Moderately Severe	2 (0.1)	0	3 (0.6)	2 (0.1)
Severe	0	0	0	0
Missing	60 (3.8)	7 (2.9)	20 (4.0)	50 (3.2)
Source: Applicant's Table 78, Pg 1421 ISS				

During conduct of the studies, 6.2% of individuals had an elevated PHQ-9 score defined as 10 or greater and 1.6% scored a positive response to Question 9. Overall, the percentages of individuals were similar between PHEN/TPM- and placebo-exposed individuals.

Table 47: Individuals with elevated PHQ-9 scores and positive Question 9 response post-randomization: 1-year cohort (safety set)

	Placebo n (%) N=1561	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)	Total N=3879 n (%)
Elevated PHQ-9 score at any time post-randomization						
≥10 (Moderate)	103 (6.6)	11 (4.6)	23 (4.6)	104 (6.6)	138 (6.0)	241 (6.2)
≥15 (Moderately severe)	13 (0.8)	3 (1.3)	2 (0.4)	23 (1.5)	28 (1.2)	41 (1.1)
≥20 (Severe)	3 (0.2)	0	1 (0.2)	7 (0.4)	8 (0.3)	11 (0.3)
Positive response to PHQ-9 Question 9 at any time post-randomization						
Yes	27 (1.7)	4 (1.7)	6 (1.2)	24 (1.5)	34 (1.5)	61 (1.6)
Source: Information request response Submission 7 Applicant Table 25, Pg 4, Applicant Table 79, Pg 1423, ISS Data from studies OB-202, DM-230, OB-302, OB-303						

The numbers and percentages of individuals with a worsening shift in PHQ-9 depression severity (from baseline to highest score) of two or more categories are shown in Table 48. Overall, there were a similar number of PHEN/TPM-exposed individuals with a worsening shift compared to the placebo-exposed individuals.

Table 48: PHQ-9 worsening depression severity score¹ 1-year cohort (safety set)

ISS one-year cohort: PHQ-9 worsening depression score					
	Placebo n (%) N=1516	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Total individuals with worsening shift	60 (3.8)	6 (2.5)	10 (2.0)	60 (3.8)	76 (3.3)
None to Moderate	48 (3.1)	3 (1.3)	9 (1.8)	41 (2.6)	53 (2.3)
None to Moderately severe	3 (0.2)	2 (0.8)	1 (0.2)	9 (0.6)	12 (0.5)
None to Severe	1 (0.1)	0	0	2 (0.1)	2 (0.08)
Mild to Moderately severe	7 (0.4)	1 (0.4)	0	3 (0.2)	4 (0.2)
Mild to Severe	1 (0.1)	0	0	4 (0.3)	4 (0.2)
Moderate to Severe	0	0	0	1 (0.1)	1 (0.04)
¹ Increase of two or more categories Source: Applicant Table 78, Pg 1421; ISS					

In the 1-year cohort the numbers and percentages of individuals with an improvement in PHQ-9 depression severity of two or more categories are shown in Table 49. Overall, there were a similar number of PHEN/TPM-exposed individuals with an improvement in PHQ-9 score compared to the placebo-exposed individuals.

Table 49: PHQ-9 improving depression severity score¹ 1-year cohort (safety set)

ISS one-year cohort: PHQ-9 improving depression score					
	Placebo N=1516 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Total individuals with improving score	4 (0.3)	0	5 (1.0)	6 (0.4)	11 (0.5)
Moderate to None	2 (0.1)	0	2 (0.4)	5 (0.3)	7 (0.3)
Moderately severe to Mild	1 (0.1)	0	2 (0.4)	1 (0.1)	3 (0.1)
Moderately severe to None	1 (0.1)	0	1 (0.2)	0	1 (0.04)
Severe to Moderate	0	0	0	0	0
Severe to Mild	0	0	0	0	0
Severe to None	0	0	0	0	0
¹ Decrease of two or more categories Source: Applicant Table 78, Pg 1421; ISS					

Because there was a higher number of depression TMEs in the PHEN/TPM-treated individuals compared to the placebo-treated individuals without obvious treatment imbalances in average PHQ-9 scores between PHEN/TPM and placebo groups, this clinical reviewer looked at the PHQ-9 scores of the persons who reported a depression-related TME. Although the incidence of events in the depression TME subclass was higher in PHEN/TPM-treated individuals compared (6.6%) to placebo-treated individuals (3.4%), overall, the severity of the depression as assessed by the PHQ-9 did not appear to differ between treatment groups.

Table 50: PHQ-9 scores for individuals with a TME in the depression subclass – 1-year cohort (safety set)

	Placebo n (%) N¹=53 n (%)	PHEN/TPM 3.75/23 N=12 n (%)	PHEN/TPM 7.5/46 N=19 n (%)	PHEN/TPM 15/92 N=121 n (%)
None	25 (47.2)	7 (58.3)	9 (47.0)	70 (58.7)
Mild	14 (26.4)	1 (8.3)	5 (26.3)	25 (19.8)
Moderate	8 (15.1)	1 (8.3)	4 (21.0)	10 (8.3)
Moderately Severe	0	1 (8.3)	0	4 (3.3)
Severe	2 (3.8)	0	0	2 (1.7)
Missing	4 (7.5)	1 (8.3)	0	10 (8.2)
Positive response Question 9	6 (11.3)	0	1 (5.3)	3 (2.5)
N is the number of individuals with a depression subclass TME Percentages calculated with the N at the top of each column Source: Applicant's Table 71, Pg 21 Response to Information request 17 May 2010 Submission 21				

Assessment of suicidality: Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS), a prospectively administered questionnaire, tracks suicidal adverse events in clinical trials. The C-SSRS assesses both suicidal behavior and ideation and provides a summary measure of suicidality. The C-SSRS was prospectively used in the Phase 3 studies with PHEN/TPM. There were no suicidal attempts, suicidal behaviors, or instances of serious suicidal ideation that occurred during study treatment (Table 51). There was a slightly higher incidence in the measure of suicidality between the PHEN/TPM-treated groups (0.8%) and placebo (0.7%) which was not statistically significant ($p=0.8901$). Although not statistically significant, a slightly higher incidence of emerging and worsening suicidal ideation occurred in the Total PHEN/TPM-treated group as compared to the placebo-treated group (Table 52).

Table 51: Study OB-302 and OB-303 C-SSRS: Number and frequency of suicidal behavior and ideation "YES" responses (safety set)

	Placebo N=1506 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1505 n (%)	PHEN/TPM Total N=2243 n (%)
Suicidality (Behavior or Ideation)	11 (0.7)	1 (0.4)	3 (0.6)	14 (0.9)	18 (0.8)
Any Suicidal Behavior	0	0	0	0	0
Actual Attempt	0	0	0	0	0
Aborted Attempt	0	0	0	0	0
Interrupted Attempt	0	0	0	0	0
Preparatory Acts or Behavior	0	0	0	0	0
Any Suicidal Ideation	11 (0.7)	1 (0.4)	3 (0.6)	14 (0.9)	18 (0.8)
Wish to be Dead	9 (0.6)	1 (0.4)	3 (0.6)	13 (0.9)	17 (0.8)
Suicidal Thoughts	5 (0.3)	1 (0.4)	1 (0.2)	6 (0.4)	8 (0.4)
Suicidal Thoughts with Methods	2 (0.1)	0	0	1 (0.1)	1 (0.04)
Ideation with intent	0	0	0	0	0
Ideation with plan and intent	0	0	0	0	0

	Placebo N=1506 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1505 n (%)	PHEN/TPM Total N=2243 n (%)
Applicant's Table 40-41, Pg 1-5 Response to information request 31 March 2010 Submission 8 Includes data from studies OB-302 and OB-303 Percentage is calculated using number of individuals in the column heading as the denominator. Individuals with multiple "Yes" responses to the same component across the study are counted only once for that component. The same subject can be counted under multiple components					

Table 52: Studies OB-302, OB-303 C-SSRS: Number and frequency of suicidality, emergence, and worsening suicidal behavior and ideation – 1-year cohort (safety set)

C-SSRS endpoint	Placebo N=1506 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1505 n (%)	PHEN/TPM total N=2243 n (%)	p-value
Emergence of suicidal ideation	7 (0.5)	1 (0.4)	2 (0.4)	13 (0.9)	16 (0.7)	0.51
Emergence of serious suicidal ideation	0	0	0	0	0	NA
Worsening suicidal ideation	7 (0.5)	1 (0.4)	2 (0.4)	14 (0.9)	17 (0.8)	0.41
Emergence of suicidal behavior	0	0	0	0	0	NA
Studies OB-302 and OB-303) Applicant's Table 40-41, Pg 1-5 Response to information request 31 March 2010 Percentage is calculated using number of individuals in the column heading as the denominator. Individuals with multiple "Yes" responses to the same component across the study are counted only once for that component. The same subject can be counted under multiple components p-value is obtained from the Fisher's Exact test for testing the response to each C-SSRS category is independent of treatment group						

Cognitive disorders TME Class

This class was subdivided into Attention, Memory impairment, Language, and Other NOS.

Attention subclass

PHEN/TPM-treated individuals were almost five times more likely to experience a TEAE related to an attention disorder compared to placebo-treated individuals. The majority of the events were mild in severity and there were no serious events within this subclass. Most PHEN-TPM-treated individuals experienced the first onset within the titration period. All except one of the adverse events were recorded as "disturbance in attention".

Memory impairment subclass

PHEN/TPM-treated individuals, in a dose-dependent manner, were three and one-half times more likely to experience a TEAE related to memory impairment compared to placebo-treated individuals. No events were considered serious and the majority of events were rated as mild in severity. Occurrence of memory impairment occurred for most individuals after the first four weeks of treatment. A slightly higher proportion of PHEN/TPM-treated compared with placebo-treated individuals who experienced a

memory-related adverse event discontinued study drug due to memory impairment (23.5% versus 20.0% in 1-year cohort).

Language subclass

Only one placebo-treated subject versus 22 PHEN/TPM-treated individuals experienced a language-related adverse event, the majority of which were aphasic events. The majority of the events were rated as mild, however within the PHEN/TPM-treated group, a third was rated as moderate and one event was rated as severe. A third of individuals in the PHEN/TPM-treated group experiencing a language-related adverse event discontinued the study drug due to the event.

Other Cognitive disorders NOS

A higher incidence of other cognitive disorders NOS occurred in the PHEN/TPM-treatment group compared to the placebo treatment group and the relationship appeared to be dose-related. The majority of the events were mild. Two PHEN/TPM-treated individuals had a severe event compared to none in the placebo group. Table 53 lists preferred terms within this subclass. The majority of events in the PHEN/TPM group were listed as a cognitive disorder or confusional state.

An additional TEAE that was not included within this other cognitive NOS subclass but is important was the general disorders organ classification of “Feeling abnormal” which occurred in three placebo individuals versus eight PHEN/TPM individuals. Table 54 lists the verbatim terms for this preferred term. All of the events except for one occurred within the first four weeks of treatment. The one exception is Subject OB-302/196-035, a 53-year-old woman who reported “feeling funny” on Day 287. Study drug was discontinued on Day 290. This subject was later diagnosed with major depression with suicidal ideation. Individuals with the “Feeling abnormal” preferred term were included in Table 44.

Table 53: Summary of other cognitive disorders NOS subclass – safety set – 1-year cohort

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Total	8 (0.5)	2 (0.8)	8 (1.6)	33 (2.1)	43 (1.9)
Cognitive disorder	1 (0.1)	0	1 (0.2)	12 (0.8)	13 (0.6)
Confusional state	3 (0.2)	2 (0.8)	2 (0.4)	8 (0.4)	12 (0.5)
Feeling abnormal	3 (0.2)	0	3 (0.6)	5 (0.3)	8 (0.3)
Bradyphrenia	0	0	2 (0.4)	5 (0.3)	7 (0.3)
Disorientation	0	0	0	2 (0.1)	2 (0.1)
Mental impairment	1 (0.1)	0	0	2 (0.1)	2 (0.1)
Source: Applicant’s Post-text Table 58; Pg 1390 ISS					

Table 54: Listing of individuals reporting the TEAE of “feeling abnormal”– 1-year cohort (safety set)

STUDY	Subject ID	Treatment	Preferred Term	Verbatim Term	Study day onset	Action taken
OB-302	194-072	Placebo	Feeling abnormal	Feeling “Fogginess”	1	None
OB-303	184-005	Placebo	Feeling abnormal	“Spacey” feeling	20	Discontinued drug
OB-303	188-082	Placebo	Feeling abnormal	“Foggy” feeling	25	None
OB-303	105-063	PHEN/TPM 7.5/46 mg	Feeling abnormal	Feeling “spaced out”	19	None
OB-303	133-021	PHEN/TPM 7.5/46 mg	Feeling abnormal	Fuzzy head	1	None
OB-303	138-136	PHEN/TPM 7.5/46 mg	Feeling abnormal	Foggy head	12	Dose reduced
OB-302	188-008	PHEN/TPM 15/92 mg	Feeling abnormal	“Spacey” feeling	11	None
OB-302	196-035	PHEN/TPM 15/92 mg	Feeling abnormal	Feeling funny	287	Drug discontinued
OB-303	109-115	PHEN/TPM 15/92 mg	Feeling abnormal	Dazed and spacey	16	Dose reduced
OB-303	157-033	PHEN/TPM 15/92 mg	Feeling abnormal	“Fuzziness” feeling in head	18	Dose reduced
OB-303	163-059	PHEN/TPM 15/92 mg	Feeling abnormal	Fogginess	19	Discontinued drug

Source: Appendix Table 16.2.7; OB-302 and OB-303 CSR

Cardiac disorders TME Class

This class was subdivided into two subclasses: cardiac arrhythmia and cardiac ischemic events.

Cardiac arrhythmia subclass

Cardiac arrhythmia related adverse events occurred with a higher frequency in mid- and high-dose PHEN/TPM treated individuals compared to placebo-treated individuals. (Table 55). The majority of events were rated as mild in severity. In the 1-year cohort eight individuals (four in the placebo group and four in the PHEN/TPM-treated group) had a serious adverse event related to a cardiac arrhythmia. The narratives for the PHEN/TPM-treated individuals are provided in Appendix E. The majority of the adverse events were related to palpitations, increased heart rate, and tachycardia. The table below summarizes the events within the cardiac arrhythmia subclass.

Table 55: Summary of cardiac arrhythmia subclass -1-year cohort (safety set)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Total	28 (1.8)	3 (1.3)	21 (4.2)	74 (4.7)	98 (4.2)
Palpitations	12 (0.8)	2 (0.8)	12 (2.4)	27 (1.7)	41 (1.8)
Heart rate increased	1 (0.1)	0	2 (0.4)	12 (0.8)	14 (0.6)
Tachycardia	1 (0.1)	1 (0.4)	2 (0.4)	11 (0.7)	14 (0.6)
Syncope	4 (0.3)	0	2 (0.4)	6 (0.4)	8 (0.3)
Atrial fibrillation	2 (0.1)	0	1 (0.2)	3 (0.2)	4 (0.2)
Syncope vasovagal	0	0	2 (0.4)	3 (0.2)	5 (0.2)
Right bundle branch block	2 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.1)
Arrhythmia	0	0	1 (0.2)	2 (0.1)	3 (0.1)
ECG abnormal	3 (0.2)	0	0	0	0
Ventricular extrasystoles	1 (0.1)	0	0	2 (0.1)	2 (0.1)
First degree AV block	1 (0.1)	0	0	1 (0.1)	1 (0.04)
ECG QT prolonged	1 (0.1)	0	0	1 (0.1)	1 (0.04)
ECG abnormal repolarization	0	0	0	2 (0.1)	2 (0.1)
Irregular heart rate	0	0	0	2 (0.1)	2 (0.1)
Loss of consciousness	0	0	1 (0.2)	1 (0.1)	2 (0.1)
Bradycardia	0	0	0	1 (0.1)	1 (0.04)
Cardiac flutter	0	0	0	1 (0.1)	1 (0.04)
Cardiorespiratory arrest	1 (0.1)	0	0	0	0
Extrasystoles	0	0	0	1 (0.1)	1 (0.04)
Sinus bradycardia	0	1 (0.4)	0	0	1 (0.04)
Sinus tachycardia	0	0	0	1 (0.1)	1 (0.04)
Supraventricular extrasystoles	0	0	1 (0.2)	0	1 (0.04)
Includes data from studies OB-202/DM-230, OB-302, and OB-303					
Source: Applicant's Table 64, Pg 1396 ISS					

Ischemic heart disease subclass

Overall, within the ischemic heart disease subclass a slightly higher percentage of events occurred within the placebo group (placebo 0.5%, PHEN/TPM total 0.3%). The majority of the events within this subclass were rated as severe. Six individuals in the placebo group (atypical angina, coronary artery disease, left main coronary disease) and five individuals in the PHEN/TPM group experienced a non-fatal serious adverse event related to cardiac ischemia defined within this subclass. An additional placebo-treated individual died of cardiorespiratory arrest. Coronary artery disease was the most

common adverse event within the placebo group and myocardial infarction was the most common adverse event within the PHEN/TPM-treated group. The tables below summarize the adverse events occurring within this subclass.

Table 56: Summary of ischemic heart disease subclass – 1-year cohort (safety set)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318
Total	8 (0.5)	1 (0.4)	3 (0.6)	4 (0.3)	8 (0.3)
Myocardial infarction	0	1 (0.4)	1 (0.2)	2 (0.1)	4 (0.2)
Angina pectoris	2 (0.1)	0	0	2 (0.1)	2 (0.1)
Coronary artery disease	5 (0.3)	0	0	1 (0.1)	1 (0.04)
Acute coronary syndrome	0	0	0	1 (0.1)	1 (0.04)
CPK increased	1 (0.1)	0	1 (0.2)	0	1 (0.04)
Arteriosclerosis coronary artery	0	0	1 (0.2)	0	1 (0.04)
Myocardial ischemia	1 (0.1)	0	0	0	0
Includes data from studies OB-202/DM-230, OB-302, and OB-303 Source: Applicant's Post-text Table 65, Pg 1398 ISS					

Table 57: Listing of non-fatal cardiac SAE – 1-year cohort (safety set)

Subject ID	Age/Race/Sex	Preferred Term	Brief Narrative
Placebo-treated			
OB-302 187-037	44/B/F	Atypical angina	Study day 78, to ED with chest pain, SOB, pain in left arm. BP 184/106, echo nml, troponin, CK-MB, stress test nml, cardiac cath right coronary artery 20% stenosis, ejection fraction 60%
OB-303 108-043	63/W/F	Coronary artery disease	Study day 28, to ED with jaw pain, angina. ECHO, stress test nml. Cardiac cath 80% focal lesion in coronary artery – stent placement
OB-303 115-018	55/W/M	Transient cardiac ischemia	Study day 242, chest pain, SOB, nausea, diaphoresis. Labs, CXR, ECG nml. Myocardial imaging inferior mild reversible abnormality, normal wall motion, ejection fraction 63%. Myocardial perfusion scan no clear evidence ischemia or prior infarct
OB-303 130-050	65/W/M	Left main coronary disease	Study day 132, exertional chest pain. Cardiac stress test, large anterosseptal area of ischemia. Mild septal hypokinesis, ejection fraction 61%. Cardiac cath significant coronary disease – underwent CABG
OB-303 151-079	48/W/M	Coronary artery disease	ED chest pain. CPK 152 U/L, troponin 0.03 ng/mL, CK-MB 2.0 ng/mL.

Subject ID	Age/Race/Sex	Preferred Term	Brief Narrative
			Cardiac cath 80% stenosis of mid left anterior – stent placement
OB-303 193-032	60/W/F	Coronary artery disease	Chest pressure. Cardiac cath – placement of three stents for coronary artery disease
PHEN/TPM treated			
OB-302 116-036	62/W/F	Myocardial infarction	On PHEN/TPM 3.75/23 Study day 58 discontinued drug. Study day 60 to ED with chest pain. Cardiac cath 80% stenosis left main coronary artery, akinesia of interventricular septum , ejection fraction 40-45%, CPK 255 U/L, CK-MB 29 U/L, peak torponin I 3.250 ng/mL – stent placement
OB-303 102-012	67/W/M	Myocardial infarction	On PHEN/TPM 7.5/46 Study day 119, after exercise, weakness, malaise. Troponin 39.67, CK-MB 61.9, ECG ST segment elevation with anterior and anteroseptal ST depression – CABG x 4
OB-303 131-042	68/W/M	Myocardial infarction	On PHEN/TPM 15/92 Study day 342, to ED with chest pain. Initial troponin 0.24 (nml) then 6.62 ng/mL then 23.22 ng/mL. cardiac cath – coronary artery disease ejection fraction 50% - CABG x6
OB-303 188-052	52/W/F	Myocardial infarction	On PHEN/TPM 15/92 Study day 174, ED with chest pain, and cardiac arrest with v-fib without pulse. ECG ST elevation precordial leads, in leads I, aVL, ST depression inferior leads. Troponin I of 11.6 mg/dL, CK-MB 23.5 ng/mL. Had revascularization of prox left anterior descending artery with stent placement
OB-303 199-037	64/W/M	Acute coronary syndrome	On PHEN/TPM 15/92 Study day 289 to ED chest pain. stress test possible reversible ischemia, ECG possible high lateral MI and second ECG anterolateral infarct (age undetermined. CK-MB 2.5 ng/mL, 2 troponin tests indeterminate
		Angina pectoris	On PHEN/TPM 15/92 Study day 362, readmitted for chest pain, elevated BP, ECG, CXR wnl. Troponin I 0.03 ng/mL. Study day 381, cardiac cath revascularized with three stents
Source: Section 14.4.3 OB-302, OB-303 CSR			

Cardiac valvulopathy

In a Phase 2 parallel group study using a 2 x 2 factorial design with the commercially available phentermine and topiramate products, 200 otherwise healthy obese individuals

(BMI ≥ 30 kg/m² to ≤ 50 kg/m²) were randomized to either placebo, phentermine 15 mg, TOPAMAX 100 mg, or the combination of Phen 15/Tpm 100 mg for 6 weeks. An echocardiogram (ECHO) was performed at baseline and at the end of the study to assess the presence of any valvular heart abnormalities.

Clinically significant valvulopathy was defined in accordance with the FDA accepted definition of cardiac valvulopathy: aortic regurgitation of mild or higher severity and mitral valve regurgitation of moderate or higher severity. There were no reports of FDA defined valvulopathy observed in any of the treatment groups. There were three individuals at Week 24 reported as having pulmonic regurgitation of mild severity. These three individuals, a 39-year-old Black woman treated with placebo, a 57-year-old Caucasian man treated with phentermine, and a 21-year-old Black man treated with topiramate did not report any adverse events during the trial and did not exhibit significantly abnormal laboratory values. The applicant was asked to provide the pulmonary artery pressures observed during the ECHO for these individuals. The sponsor did not have access to this information and therefore pulmonary arterial pressures for these individuals are not known. A trivial or mild degree of pulmonic regurgitation is detectable in most normal individuals and most often has a benign clinical course.⁴² No other echocardiographic measurements were performed in the PHEN/TPM development program.

Ophthalmic disorders Class

Acute myopia and secondary angle closure glaucoma are listed in the warnings and precautions section of the topiramate label. Individuals in the PHEN/TPM studies were asked at every study visit if they had experienced any eye pain or sudden changes in vision since their previous visit. Within the PHEN/TPM development program there was a higher incidence of TEAEs within the ophthalmic disorder class in PHEN/TPM-treated individuals compared to placebo-treated individuals. The majority were rated as mild in severity and occurred after the first four weeks of treatment. No events were listed as serious. The majority of the adverse events were related to eye pain. The adverse events within this class are summarized below.

Table 58: Summary of ophthalmic disorder class - 1-year cohort (safety set)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Total	27 (1.7)	6 (2.5)	12 (2.4)	39 (2.5)	57 (2.5)
Eye pain	22 (1.4)	5 (2.1)	11 (2.2)	35 (2.2)	51 (2.2)
Glaucoma	1 (0.1)	1 (0.4)	0	2 (0.1)	3 (0.1)
Myopia	2 (0.1)	0	0	2 (0.1)	2 (0.1)
Intraocular pressure increased	1 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.1)
Open angle glaucoma	1 (0.1)	0	0	0	0

⁴² Bruce CB et al. Right-sided valve disease deserves a little more respect. Circulation 2009;119: 2726-34

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Data from studies OB-202/DM-230, OB-302, and OB-303 Source: Applicant's Table 61, Pg 1393 ISS					

Psychomotor disorders Class

Although overall the number of individuals reporting a treatment-emergent adverse event within the psychomotor disorder class was small, individuals treated with PHEN/TPM were eight times more likely to report a psychomotor disorder compared to individuals treated with placebo. The majority of events were mild, however six events in the PHEN/TPM group were rated moderate or severe compared to none in the placebo group. No events were listed as serious. Individuals were likely to experience an event within the first four weeks of treatment. The most common adverse event reported in all treatment groups was psychomotor hyperactivity.

Drug Abuse/withdrawal Class

There were no TEAEs within this class reported in the 1-year cohort for any of the treatment groups. However, there was one treatment-emergent adverse event reported as "disturbance in social behavior" within the Drug Abuse subclass in a subject treated with mid-dose PHEN/TPM in the 6-month OB-301 study.

The Agency Controlled Substances Staff (CSS) provided the applicant with an additional list of terms grouped into "Euphoria-related terms," "Terms related to impaired attention, Psychomotor Event, Cognition, and Mood", and "Dissociative and Psychotic terms". A full listing of the preferred and verbatim terms are provided in Appendix F. The results of the CSS specified categories are described in Table 59.

Table 59: Summary of CSS-specified terms for abuse potential assessment

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)
Euphoria-related	57 (3.7)	7 (2.9)	40 (8.0)	148 (9.4)
Attention, psychomotor, cognition, mood	45 (2.9)	9 (3.8)	36 (7.2)	172 (10.9)
Dissociative and Psychotic	8 (0.5)	3 (1.3)	8 (1.6)	29 (1.8)
Source: Applicant's Table 8, Pg 35; VI0521-ABUSE-01 study report				

In PHEN/TPM-treated individuals there appeared to be a dose-related response in all categories. The most common adverse event reported in the euphoria-related class was "dizziness", followed by "feeling abnormal". Four subjects experienced a euphoric mood (1 placebo, 3 PHEN/TPM) and 5 subjects treated with high-dose PHEN/TPM experienced a hallucination. The narratives of these individuals are provided in Appendix G. There were no overdoses reported in the PHEN/TPM clinical development program. Phentermine is currently controlled as a Schedule IV (non-narcotic) drug.

Other safety topics of interest

Metabolic acidosis

Metabolic acidosis is labeled in the warnings and precautions section of the topiramate label. As defined by a treatment-emergent adverse event, metabolic acidosis and acidosis-related AEs were uncommon within PHEN/TPM's integrated safety summary. Only one PHEN/TPM-treated subject reported metabolic acidosis in the 6-month cohort and two high-dose PHEN/TPM-treated individuals in the 1-year cohort.

Fasting blood chemistries including bicarbonate were evaluated at screening and at weeks 4, 8, 16, 28, 40, and at the end of treatment. There were no arterial blood gases obtained within the PHEN/TPM development. There were no established intervention procedures for bicarbonate values less than 21 mEq/L. The applicant reported mean changes in serum bicarbonate of an approximately 2 mEq/L decrease for the PHEN/TPM-exposed individuals as compared to a 0.2 mEq/L decrease in the placebo- exposed individuals. The applicant claims that the mean decreases in serum bicarbonate from baseline for the PHEN/TPM groups are not clinically meaningful.

It is this clinical reviewer's opinion, however, that looking at central tendency measures does not convey the clinically significant bicarbonate reductions observed with this drug. An analysis that accounts for individuals that obtain a categorically subnormal level of bicarbonate while on PHEN/TPM may describe a more clinically relevant picture. Therefore, the applicant was asked to conduct several additional analyses regarding the number and frequency of individuals with a subnormal serum bicarbonate using the cutoffs of <21 mEq/L and <17 mEq/L at any time and persistently (Table 60) while on study drug which was similar to analyses performed with TOPAMAX. Persistence was defined as two consecutive visits below the given threshold or a value below the given threshold at the final visit

There is evidence suggestive of a dose-response relationship in PHEN/TPM-exposed individuals for low serum bicarbonate values. In the 1-year cohort, 27% of PHEN/TPM-treated individuals experienced at least one serum bicarbonate less than 21 mEq/L while on study drug versus 5.9% of placebo-treated individuals. For reference, the most common TEAE was paresthesia at roughly 20% of the PHEN/TPM population which may also be related to metabolic acidosis.

Table 60: Summary of abnormal bicarbonate values during the double-blind treatment phase (1-year cohort)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	Any PHEN/TPM N=2318 n (%)
Summary of abnormal serum bicarbonate values during double-blind treatment period (1-year cohort)					
Serum bicarbonate <21mEq/L					
Any time post-randomization	92 (5.9)	39 (16.3)	112 (22.5)	474 (30.0)	625 (27.0)
At Final Visit	28 (1.8)	13 (5.4)	18 (3.6)	124 (7.8)	155 (6.7)
During titration phase	34 (2.2)	18 (7.5)	42 (8.4)	240 (15.2)	300 (12.9)

Summary of abnormal serum bicarbonate values during double-blind treatment period (1-year cohort)	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	Any PHEN/TPM N=2318 n (%)
During maintenance phase	66 (4.2)	31 (12.9)	88 (17.7)	355 (22.5)	474 (20.4)
Persistence ^[1]	33 (2.1)	21 (8.8)	32 (6.4)	203 (12.8)	256 (11.0)
Serum bicarbonate <17 mEq/L					
Any time post-randomization	4 (0.3)	4 (1.7)	8 (1.6)	31 (2.0)	43 (1.9)
At final visit	1 (0.1)	3 (1.3)	0	7 (0.4)	10 (0.4)
During titration phase	1 (0.1)	0	3 (0.6)	12 (0.8)	15 (0.6)
During maintenance phase	3 (0.2)	4 (1.7)	6 (1.2)	23 (1.5)	33 (1.4)
Persistence	1 (0.1)	3 (1.3)	1 (0.2)	11 (0.7)	14 (0.6)
Includes data from studies OB-202, DM-230, OB-302, and OB-303 ¹ Persistence is defined as two consecutive visits below the given threshold or a value below the given threshold at the final visit Source: Applicant's Table 2.1 Response to IR 17 May 2010 Submission 22					

The current TOPAMAX label states topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated. In the PHEN/TPM 1-year safety cohort, there were 246 (10.6%) individuals treated with metformin and PHEN/TPM. Table 61 lists the incidence of low bicarbonate values reported within this group.

Table 61: Incidence of low bicarbonate and related adverse events in individuals treated with metformin – 1-year cohort (safety set)

Summary of abnormal serum bicarbonate values during double-blind treatment period (1-year cohort)	Placebo n (%) N=1561	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)	PHEN/TPM Total N=2318 n (%)
Subjects taking metformin at any time	184 (11.8)	2 (0.83)	49 (9.8)	195 (12.3)	246 (10.6)
Serum bicarbonate <21mEq/L	12 (6.5)	1 (50.0)	9 (18.4)	57 (29.2)	67 (27.2)
Serum bicarbonate <17 mEq/L	0	0	1 (2.0)	5 (2.6)	6 (2.4)
Persistent bicarbonate <21 mEq/L	6 (3.3)	0	3 (6.1)	25 (12.8)	28 (11.4)
Persistent bicarbonate <17 mEq/L	0	0	1 (2.0)	1 (0.5)	2 (0.8)
Includes data from studies OB-202/DM-230, OB-302, and OB-303 Persistence is defined as two consecutive visits below the given threshold or a value below the given threshold at the final visit Metformin use within 30 days of the first abnormal bicarbonate value Source: Applicant's Table 3.4 Response to IR 17 May 2010 Submission 22					

Vital Signs assessment

Vital signs were assessed at each study visit. Measurements were made after individuals had been seated comfortably for at least 10 minutes. Blood pressure was measured using a calibrated sphygmomanometer with an appropriately sized cuff. Pulse rate was

assessed over a 30-second period. Wherever possible, the same person was to have performed all assessments for a given individual.

Blood pressure

Mean systolic and diastolic blood pressure decreased in all treatment groups, but to a larger extent in the PHEN/TPM groups. In terms of categorical increases in systolic and diastolic blood pressure, the PHEN/TPM groups had a lower frequency compared to the placebo group. Twenty-four hour ambulatory blood pressure monitoring was not performed.

Table 62: Mean changes in blood pressure (mmHg) from baseline - 1-year cohort (safety set)

	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Number of individuals with baseline and endpoint measurements	n=1532	n=234	n=488	n=1553
Systolic blood pressure (mmHg)				
Baseline mean (SD)	126.5 (13.25)	122.5 (11.11)	128.5 (13.63)	125.7 (13.12)
Mean change (SD)	-2.1 (14.01)	-3.3 (11.95)	-5.2 (14.77)	-5.2 (14.48)
Diastolic blood pressure (mmHg)				
Baseline mean (SD)	79.6 (8.95)	77.8 (7.49)	80.6 (8.71)	79.0 (8.76)
Mean change (SD)	-1.9 (9.61)	-0.9 (8.29)	-3.3 (9.87)	-2.9 (9.40)
Data from studies OB-202/DM-230, OB-302, and OB-303				
Source: Applicant's Table 35, Pg 118; ISS				

Table 63: Summary of categorical increases in blood pressure (mmHg) during double-blind treatment-safety set - 1-year cohort (safety set)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 N (%)	PHEN/TPM 15/92 N=1580 n (%)
Systolic blood pressure				
>5 mmHg	1033 (66.2)	141 (58.8)	289 (58.0)	923 (58.4)
>10 mmHg	733 (47.0)	101 (42.1)	182 (36.5)	645 (40.8)
>15 mmHg	506 (32.4)	71 (29.6)	132 (26.5)	436 (27.6)
>20 mmHg	295 (18.9)	29 (12.1)	79 (15.9)	235 (14.9)
>25 mmHg	180 (11.5)	16 (6.7)	49 (9.8)	134 (8.5)
>30 mmHg	86 (5.5)	9 (3.8)	26 (5.2)	63 (4.0)
Diastolic blood pressure				
>5 mmHg	891 (57.1)	141 (58.8)	280 (56.2)	855 (54.1)
>10 mmHg	465 (29.8)	76 (31.7)	147 (29.5)	469 (29.7)
>15 mmHg	247 (15.8)	35 (14.6)	63 (12.7)	234 (14.8)
>20 mmHg	100 (6.4)	10 (4.2)	27 (5.4)	81 (5.1)
Data from studies OB-202/DM-230, OB-302, and OB-303 are included.				
All measurements during the double-blind treatment period are considered.				
Source: Applicant's Table 36, Pg 119 ISS				

Heart rate

Mean heart rate was increased in all PHEN/TPM-treatment groups compared to the placebo-treatment group. Overall, PHEN/TPM-treated groups had a higher frequency of categorical increases in heart rate compared to the placebo groups. The largest increases were observed in individuals treated with high-dose PHEN/TPM.

Table 64: Mean changes in heart rate (bpm) from baseline – 1-year cohort (safety set)

	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Heart rate (bpm)				
n [1]	1532	234	488	1553
Baseline mean (SD)	72.5 (9.58)	72.3 (9.22)	72.2 (10.07)	72.7 (9.87)
Mean change (SD)	0 (10.19)	1.3 (10.32)	0.6 (10.18)	1.6 (10.28)
Data from studies OB-202/DM-230, OB-302, and OB-303 are included. [1] n is the number of individuals with baseline and endpoint measurements All measurements during the double-blind treatment period are considered. Source: Applicant's Table 35, Pg 118ISS				

Table 65: Summary of categorical increases in heart rate (bpm) during double-blind treatment – 1-year cohort (safety set)

	Placebo N=1561 n (%)	PHEN/TPM 3.75/23 N=240 n (%)	PHEN/TPM 7.5/46 N=498 n (%)	PHEN/TPM 15/92 N=1580 n (%)
Heart rate				
>5 bpm	1021 (65.4)	168 (70.0)	372 (74.7)	1228 (77.7)
>10 bpm	657 (42.1)	120 (50.0)	251 (50.4)	887 (56.1)
>15 bpm	410 (26.3)	79 (32.9)	165 (33.1)	590 (37.3)
>20 bpm	186 (11.9)	36 (15.0)	67 (13.5)	309 (19.6)
Source: Applicant's Table 36, Pg 119 ISS				

Pregnancy

In the PHEN/TPM clinical development program, women of childbearing potential were eligible for enrollment in clinical studies. Participation required agreement to use double-barrier contraception or be on stable hormonal contraception and use a single-barrier method. Barrier methods considered acceptable were intrauterine device, condom (male or female), cervical cap, and spermicide. Monthly urine pregnancy testing was performed on all women of childbearing potential.

By June 2008 (first Phase 3 trial began November 2007), there were 12 confirmed pregnancies. Additional measures to minimize pregnancy risk were implemented which included sharing information regarding the risks and documented cases of teratogenicity with topiramate, as defined in the label and literature, contraceptive education and review of compliance requirements, including a reaffirmation of their willingness to comply with study-mandated contraceptive requirements in order to continue in the study.

Additionally, a revised Investigator Brochure was provided to all the sites, with updated information concerning potential risks of teratogenicity. Regardless of these varied

attempts to mitigate pregnancy exposure, an additional 22 pregnancies occurred for a total of 34 pregnancies within the development program. When a pregnancy became known, individuals were to stop study drug and were discontinued from study participation. The pregnancy was monitored until resolution by the applicant.

The average estimated gestational age at pregnancy diagnosis was 5.4 weeks for the pregnancies where dating information was available by quantitative serum beta human chorionic gonadotropin or ultrasound. The table below summarizes the pregnancies by study and treatment regimen. The majority of pregnancies occurred in PHEN/TPM-treated individuals.

Table 66: Frequency of pregnancies in PHEN/TPM clinical development pregnancy by study and treatment group

Study	Total	Placebo	Active Comparator	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92	PHEN/TPM Total
OB-118 [1]	1	0	–				1
OB-205 [1]	2	0	–				2
OB-301	8	1	5 [2]	–	2	–	2
OB-302	18	3	–	1	–	14	15
OB-303	3	0	–	–	1	2	3
OB-305 [3]	2		–	–			
Program	34	4	5	1	3	16	23
1. Active treatment, unable to determine dose due to study design. 2. TPM46 (1), PHEN15 (2), and TPM92 (2). 3. Study is still blinded. Total count includes 32 cases. OB-305 cases not included in treatment group counts. PHEN = phentermine; TPM = topiramate; PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate.							

The source documents of all the pregnancies were reviewed including the newborn examination form completed by the applicant. Of the 34 pregnancies, 18 were carried to term (one pregnancy was ongoing), six pregnancies were spontaneously aborted, six pregnancies were electively terminated, one pregnancy outcome was unknown, one pregnancy was ectopic, and one pregnant woman was lost to follow up (Table 67). None of the 18 pregnancies carried to term were reported to have any congenital anomalies.

Table 67: Listing of pregnancies occurring in PHEN/TPM clinical development program

Study #	Subject ID	Treatment	Maternal age at conception	Date of pregnancy diagnosis	Date of first dose	Date of last dose	Contraception method	Final status of pregnancy	Pregnancy outcome
118	2056-485	Active treatment, unable to determine dose due to study design	29	4/2/2009	3/10/2009	3/30/2009	Unknown	Ectopic pregnancy	NA
205	026-304	Active treatment, unable to determine dose due to study design	36	3/14/2009	2/21/2009	3/13/2009	Condoms/spermicide	Spontaneous abortion	NA
205	018-165	Active treatment, unable to determine dose due to study design	35	4/2/2009	2/6/2009	4/1/2009	Condoms/spermicide	Delivered	Normal
301	121-005	Placebo	28	3/25/2008	1/11/2008	3/14/2008	Condoms/spermicide	Elective termination	NA
301	114-012	Phen 15 mg	29	2/14/2008	2/6/2008	3/14/2008	Condoms/spermicide	Elective termination	NA
301	117-013	Phen 15 mg	33	6/6/2008	1/9/2008	6/5/2008	Condoms/spermicide	Delivered	Normal
301	111-010	TPM 46 mg	31	5/2/2008	1/28/2008	5/16/2008	Condoms/spermicide	Delivered	Normal
301	102-046	TPM 92 mg	34	7/31/2008	2/13/2008	7/30/2008	Condoms/spermicide	Delivered	Normal
301	133-024	TPM 92 mg	36	8/27/2008	2/29/2008	8/20/2008	OCP/condoms	Unknown	NA
301	106-024	PHEN/TPM 7.5/46	37	2/29/2008	2/4/2008	2/29/2008	Unknown	Lost to follow-up	NA
301	133-015	PHEN/TPM 7.5/46	32	8/13/2008	2/26/2008	8/4/2008	Condoms/spermicide	Delivered	Normal
302	109-042	PHEN/TPM	36	7/22/2008	1/18/2008	7/21/2008	Condoms	Delivered	Normal

Study #	Subject ID	Treatment	Maternal age at conception	Date of pregnancy diagnosis	Date of first dose	Date of last dose	Contraception method	Final status of pregnancy	Pregnancy outcome
		3.75/23							
302	202-006	PHEN/TPM 15/92	29	1/9/2008	12/12/2007	1/8/2008	OCP/condoms	Delivered	Normal
302	187-048	PHEN/TPM 15/92	24	3/28/2008	1/25/2008	3/26/2008	Condoms/spermicide	Spontaneous abortion	NA
302	100-018	PHEN/TPM 15/92	32	4/2/2008	11/29/2007	3/26/2008	Unknown	Elective termination	NA
302	148-018	PHEN/TPM 15/92	23	4/3/2008	1/10/2008	4/2/2008	OCP/Condoms	Delivered	Normal
302	196-021	PHEN/TPM 15/92	23	6/27/2008	12/19/2007	6/26/2008	Condoms/spermicide	Delivered	Normal
302	173-019	PHEN/TPM 15/92	32	7/16/2008	1/4/2008	7/15/2008	Condoms/spermicide	Spontaneous abortion	NA
302	162-052	PHEN/TPM 15/92	26	7/22/2008	4/1/2008	7/21/2008	OCP/condoms	Spontaneous abortion	NA
302	197-016	PHEN/TPM 15/92	29	7/16/2008	2/8/2008	7/5/2008	Condoms/spermicide	Delivered	Normal
302	176-011	PHEN/TPM 15/92	30	7/29/2008	12/10/2007	7/29/2008	OCP/condoms	Delivered	Normal
302	147-025	PHEN/TPM 15/92	29	8/13/2008	1/2/2008	7/29/2008	OCP/Condoms	Delivered	Normal
302	106-004	PHEN/TPM 15/92	20	10/17/2008	1/11/2008	10/17/2008	Condoms/spermicide	Elective termination	NA
302	148-046	PHEN/TPM 15/92	34	1/5/2009	2/1/2008	1/4/2009	OCP/condoms	Delivered	Normal
302	132-038	PHEN/TPM 15/92	18	11/26/2008	3/26/2008	11/25/2008	Condoms/spermicide	Spontaneous abortion	NA
302	201-042	Placebo	33	5/1/2008	1/21/2008	4/25/2008	OCP/condoms	Delivered	Normal
302	148-004	Placebo	33	9/19/2008	12/14/2007	9/17/2008	Sponge/spermicide	Delivered	Normal
302	118-023	Placebo	28	12/23/2008	1/22/2008	11/23/2008	OCP/condoms	Delivered	Normal
302	137-003	PHEN/TPM 15/92	40	1/22/2009	12/21/2007	12/11/2008	Condoms/spermicide	Delivered	Normal
303	181-023	PHEN/TPM	21	5/16/2008	1/31/2008	5/13/2008	OCP	Delivered	Normal

Study #	Subject ID	Treatment	Maternal age at conception	Date of pregnancy diagnosis	Date of first dose	Date of last dose	Contraception method	Final status of pregnancy	Pregnancy outcome
		7.5/46							
303	177-033	PHEN/TPM 15/92	37	10/22/2008	3/6/2008	10/22/2008	OCP/condoms	Elective termination	NA
303	100-003	PHEN/TPM 15/92	30	11/13/2008	11/20/2007	11/17/2008	Condom/spermicide	Elective termination	NA
305	167-123	Placebo	38	8/19/2009	4/22/2009	8/18/2009	OCP/condom Condom/spermicide	Spontaneous abortion	NA
305	162-063	PHEN/TPM 15/92	27	10/5/2009	5/21/2009	9/24/2009	OCP/condoms	Ongoing	Ongoing
Source: Pregnancy source documents: Submission 6									

Appendices

Appendix A: Listing of preferred terms used in grouping of Targeted Medical Events by Class and Subclass

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
Cardiac Disorders	Cardiac Arrhythmia	
		AV dissociation
		Accelerated idioventricular rhythm
		Accessory cardiac pathway
		Adams-Stokes syndrome
		Agonal rhythm
Psychiatric Disorders	Sleep Disorders	Dysomnia
		Early morning awakening
		Hypersomnia
		Hyposomnia
		Initial insomnia
		Insomnia
		Middle insomnia
		Poor quality sleep
		Somnolence
	Anxiety	Agitation
		Anxiety
		Irritability
	Depression	Activation syndrome
		Adjustment disorders with depressed mood
		Adjustment disorder with mixed anxiety and depressed mood
		Affect lability
		Agitated depression
		Alcohol abuse
		Alcohol problem
		Alcohol rehabilitation
		Alcoholism
		Anhedonia
		Antidepressant therapy
		Apathy
		Blunted affect
		Constricted affect
		Crying
		Decreased interest
		Depressed mood
		Depression
		Depression postoperative
		Depressive symptom
		Dysphoria
		Dysthymic disorder
		Electroconvulsive therapy
		Emotional distress

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Feeling guilty
		Feeling of despair
		Feelings of worthlessness
		Impaired self-care
		Listless
		Major depression
		Menopausal depression
		Mood altered
		Mood swings
		Morose
		Negative thoughts
		Neglect of personal appearance
		Psychosocial support
		Psychotherapy
		Self esteem decreased
		Tearfulness
	Suicide/Self-injury	Completed suicide
		Depression suicidal
		Intentional overdose
		Intentional self-injury
		Multiple drug overdose intentional
		Poisoning deliberate
		Self injurious behavior
		Self injurious ideation
		Suicidal behavior
		Suicidal ideation
		Suicide attempt
Cognitive Disorders	Attention	Change in sustained attention
		Disturbance in attention
	Memory Impairment	Amnesia
		Memory impairment
	Language	Aphasia
		Difficulty with language
		Dysarthria
		Dysphasia
	Other Cognitive NOS	Borderline mental impairment
		Bradyphrenia
		Cognitive disorder
		Cognitive impairment
		Confusional state
		Disorientation
		Dyscalculia
		Judgement impaired
		Mental impairment
		Thinking abnormal
Cardiac disorders	Cardiac arrhythmia	AV dissociation
		Accelerated idioventricular rhythm
		Accessory cardiac pathway
		Adams-Stokes syndrome
		Agonal rhythm
		Anomalous AV excitation

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Arrhythmia
		Arrhythmia neonatal
		Arrhythmia supraventricular
		Arrhythmogenic right ventricular dysplasia
		Atrial conduction time prolongation
		Atrial fibrillation
		Atrial flutter
		Atrial tachycardia
		AV block
		AV block complete
		AV block first degree
		AV block second degree
		AV conduction time shortened
		AV extrasystoles
		Bifascicular block
		Bradycardia
		Bradycardia fetal
		Bradycardia neonatal
		Brugada syndrome
		Bundle branch block
		Bundle branch block bilateral
		Bundle branch block left
		Bundle branch block right
		Cardiac arrest
		Cardiac arrest neonatal
		Cardiac death
		Cardiac fibrillation
		Cardiac flutter
		Cardiac telemetry abnormal
		Cardiorespiratory arrest
		Cardiorespiratory arrest neonatal
		Conduction disorder
		ECG P wave inverted
		ECG P wave abnormal
		ECG PQ interval prolonged
		ECG PR prolongation
		ECG QRS complex prolonged
		ECG QT prolonged
		ECG RR interval prolonged
		ECG U-wave abnormality
		ECG U-wave biphasic
		ECG abnormal
		ECG ambulatory abnormal
		ECG change
		ECG delta waves abnormal
		ECG repolarization abnormality
		Electromechanical dissociation
		Extrasystoles
		Fetal arrhythmia

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Fetal heart rate deceleration
		Fetal heart rate disorder
		Gallop rhythm present
		Heart alternation
		Heart block congenital
		Heart rate abnormal
		Heart rate decreased
		Heart rate increased
		Heart rate irregular
		Long QT syndrome
		Long QT syndrome congenital
		Loss of consciousness
		Lown-Ganong-Levine syndrome
		Neonatal tachycardia
		Nodal arrhythmia
		Nodal rhythm
		Pacemaker generated arrhythmia
		Palpitations
		Parasystole
		Paroxysmal arrhythmia
		Reperfusion arrhythmia
		Rhythm idioventricular
		Sick sinus syndrome
		Sinoatrial block
		Sinus arrest
		Sinus arrhythmia
		Sinus bradycardia
		Sinus tachycardia
		Sudden cardiac death
		Sudden death
		Supraventricular extrasystoles
		Supraventricular tachyarrhythmia
		Supraventricular tachycardia
		Syncope
		Syncope vasovagal
		Tachyarrhythmia
		Tachycardia
		Tachycardia fetal
		Tachycardia paroxysmal
		Torsade de pointes
		Trifascicular block
		Ventricular arrhythmia
		Ventricular asystole
		Ventricular extrasystoles
		Ventricular fibrillation
		Ventricular flutter
		Ventricular pre-excitation
		Ventricular tachyarrhythmia
		Ventricular tachycardia
		Wandering pacemaker
		Withdrawal arrhythmia

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Wolff-Parkinson-White syndrome
		Wolff-Parkinson-White syndrome congenital
	Ischemic heart disease	Acute coronary syndrome
		Acute myocardial infarction
		Angina pectoris
		Angina unstable
		Arteriogram coronary abnormal
		Arteriosclerosis coronary artery
		Arteriospasm coronary
		CPK MB abnormal
		CPK MB increased
		CPK increased
		Cardiac enzymes increased
		Cardiac stress test abnormal
		Computerized tomogram coronary artery abnormal
		Coronary angioplasty
		Coronary arterial stent insertion
		Coronary artery bypass
		Coronary artery disease
		Coronary artery dissection
		Coronary artery embolism
		Coronary artery insufficiency
		Coronary artery occlusion
		Coronary artery reocclusion
		Coronary artery stenosis
		Coronary artery thrombosis
		Coronary endarterectomy
		Coronary ostial stenosis
		Coronary revascularization
		Dissecting coronary artery aneurysm
		ECG signs of myocardial ischemia
		ECG Q wave abnormal
		ECG ST segment abnormal
		ECG ST segment depression
		ECG ST segment elevation
		ECG ST-T segment abnormal
		ECG ST-T segment depression
		ECG ST-T segment elevation
		Exercise ECG abnormal
		Exercise test abnormal
		External counter pulsation
		Hemorrhage coronary artery
		In-stent coronary artery restenosis
		Infarction
		Ischemic cardiomyopathy
		Microvascular angina
		Myocardial infarction
		Myocardial ischemia
		Myocardial reperfusion injury

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Papillary muscle infarction
		Percutaneous coronary intervention
		Post-procedural myocardial infarction
		Postinfarction angina
		Prinzmetal angina
		Scan myocardial perfusion abnormal
		Silent myocardial infarction
		Stress cardiomyopathy
		Subclavian coronary steal syndrome
		Subendocardial ischemia
		Troponin I increased
		Troponin T increased
		Troponin increased
		Vascular graft occlusion
Ophthalmic disorders	Ophthalmic disorders	Angle closure glaucoma
		Eye pain
		Glaucoma
		Intraocular pressure increased
		Myopia
		Open angle glaucoma
Menstrual disorders	Menstrual disorders	Amenorrhea
		Hypomenorrhea
		Menometrorrhagia
		Menorrhagia
		Menstruation irregular
		Metrorrhagia
		Oligomenorrhea
		Vaginal hemorrhage
Psychomotor disorders	Psychomotor disorders	Ataxia
		Bradykinesia
		Coordination abnormal
		Dyskinesia
		Gait disturbance
		Hypervigilance
		Psychomotor hyperactivity
		Psychomotor retardation
Drug Abuse/withdrawal class	Drug abuse subclass	Accidental overdose
		Dependence
		Disturbance in social behavior
		Drug abuse
		Drug abuser
		Drug administered at inappropriate site
		Drug dependence
		Drug dependence, antepartum
		Drug dependence, postpartum
		Drug detoxification
		Drug level above therapeutic
		Drug level increased
		Drug screen

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Drug screen positive
		Drug tolerance
		Drug tolerance decreased (or hypersensitivity)
		Drug tolerance increased
		Drug toxicity
		Intentional drug misuse
		Multiple drug overdose
		Multiple drug overdose
		Multiple drug overdose accidental
		Needle track marks
		Neonatal complications of substance abuse
		Overdose
		Polysubstance dependence
		Substance abuse
		Substance abuser
		Therapeutic agent toxicity
	Drug Withdrawal subclass	Drug rehabilitation
		Drug withdrawal convulsions
		Drug withdrawal headache
		Drug withdrawal maintenance therapy
		Drug withdrawal syndrome
		Drug withdrawal syndrome neonatal
		Rebound effect
		Steroid withdrawal syndrome
		Withdrawal arrhythmia
		Withdrawal syndrome

Appendix B: Myocardial infarction narratives

Subject OB 302/116-036 [PHEN/TPM 3.75/23] myocardial infarction

62-year-old White female with a history of hypertension, dyslipidemia, coronary artery disease was randomized to PHEN/TPM 3.75/23 mg. On Study Day 58, she discontinued study medication. On Study Day 60, she presented to the hospital with complaints of significant chest pain and was diagnosed with a myocardial infarction by laboratory testing and cardiac catheterization. Treatment included a percutaneous coronary intervention with a drug eluting stent. The subject withdrew consent and completed the last study visit on Study Day 148.

Subject OB 303/102-012 [PHEN/TPM 7.5/46 mg]: myocardial infarction

67-year-old White male with a history of obesity was randomized to PHEN/TPM 7.5/46 mg on (b) (4). On Study Day 119 (b) (4), after pushing a hand mower about 150 feet, the subject became lightheaded and had no energy and was admitted to the hospital with a 2-day history of weakness, malaise, and some epigastric discomfort. An initial troponin was elevated at 39.67 with a creatine phosphokinase (CK) and CK-MB of 783 and 61.9, respectively (units and normal ranges not reported). An

electrocardiogram revealed inferior ST segment elevation with anterior and anteroseptal ST depression. The subject was subsequently diagnosed with a myocardial infarction. A coronary angiography demonstrated severe multi-vessel coronary artery disease with an occluded right posterolateral branch. During the angiography, the subject developed hemodynamic instability including heart block requiring placement of a temporary pacemaker and hypotension requiring intravenous dopamine and placement of an intrathoracic balloon pump. Treatment of the event included emergent bypass grafting times four with the left internal mammary artery to the left anterior descending coronary artery and reverse autogenesis saphenous vein grafts to the second obtuse marginal, right posterior descending artery, and right posterolateral arteries. The study drug was permanently discontinued on Study Day 119 (b) (4). The subject recovered from the event and was discharged from the hospital on Study Day 124 (b) (4). The subject continued in the study off study drug. The subject's medical history includes past tobacco use (cigarettes), dyslipidemia, diabetes, chronic constipation, enlarged prostate, prosthetic left eye, multiple missing teeth, burn scar left lower forearm, peripheral neuropathy, erectile dysfunction, stage II cataract, upper gastrointestinal ulcer, left upper arm fracture, enucleation of left eye, appendectomy, vasectomy, and choroidal melanoma (left eye). Concomitant medications included aspirin, chromium picolinate, tamsulosin, and metformin.

Subject OB 303/188-052 [PHEN/TPM 15/92 mg]: myocardial infarction

52-year-old Caucasian female with a history of obesity was randomized to PHEN/TPM 15/92 mg on (b) (4). On Study Day 174 (b) (4), the subject developed chest pain and was transported to the hospital via emergency medical services. During transport, the subject experienced a seizure and subsequently developed ventricular fibrillation without a pulse. Cardiopulmonary resuscitation was initiated. The subject reportedly experienced ventricular fibrillation or pulseless electrical activity for 23 to 24 minutes. On admission, blood pressure was 140/70 mmHg and pulse was 122 bpm. The subject was decorticating, unresponsive, and intubated. A computerized tomography of the head performed on arrival to the emergency room revealed no bleeding and no gross abnormalities. An electrocardiogram showed ST elevation in the precordial leads, in leads I, aVL, and ST depression of the inferior leads. Laboratory results revealed a troponin I of 11.6 mg/dL, creatine phosphokinase (CK) of 490 U/L, and CK-MB of 23.5 ng/mL. The subject was subsequently diagnosed with a myocardial infarction. On Study Day 175 (b) (4), the subject underwent an echocardiogram, which showed mildly reduced left ventricular systolic dysfunction with regional wall motion abnormalities, distal anterior and mid to distal septal walls consistent with infarct, mild concentric left ventricular hypertrophy, and evidence of diastolic dysfunction. On Study Day 176 (b) (4), the subject underwent revascularization of the proximal left anterior descending artery with drug-eluting stent placement. Additional treatment of the event included abciximab, heparin, furosemide, clopidogrel, and diazepam. The subject recovered with sequelae from the event and was discharged from the hospital on Study Day 180 (b) (4). The study drug was permanently discontinued on Study Day 174 (b) (4). The subject continued in the study off study drug and was lost to follow-up and hence discontinued from the study on Study Day 257 (b) (4). The subject's medical history includes current tobacco use (cigarettes), hypertension, laser

vision correction, sleep apnea, umbilical hernia, gastroesophageal reflux disease, routine colonoscopy, right breast cyst, hysterectomy, bilateral tubal ligation, hot flashes, tension headaches, joint pain bilateral wrists, trouble sleeping, cervical laminectomy, tonsillectomy, heel spur, cardiac catheterization-negative, right ring finger fracture, and seasonal allergic rhinitis. Concomitant medications included esomeprazole, Hyzaar, diclofenac sodium, and multivitamins.

Subject OB 303/131-042 [PHEN/TPM 15/92 mg]: myocardial infarction

68-year-old White male with a history of obesity was randomized to PHEN/TPM 15/92 mg on (b) (4). On Study Day 342 (b) (4), the subject presented to the emergency room after having an episode of chest pain. On Study Day 343 (b) (4), initial troponin was 0.24 (normal range, <0.10 ng/mL) and subsequent troponin was 6.62 ng/mL at 6:45 and 23.22 ng/mL at 23:18. The subject was subsequently transferred to another hospital and underwent a cardiac catheterization, which revealed triple vessel coronary artery disease and a left ventricular ejection fraction of 50%. On Study Day 344 (b) (4), at 7:30, troponin was 17.41 ng/mL. A diagnosis of myocardial infarction was made. On Study Day 344 (b) (4), the subject was transferred to another hospital for further evaluation and treatment. On that same date, an electrocardiogram showed normal sinus rhythm with a ventricular rate of 64 bpm. On Study Day 345 (b) (4), the subject underwent an off-pump coronary artery bypass graft surgery times six with intramyocardial ramus branch. Treatment of the event included potassium, oxygen at 2 liters via nasal cannula, Lorcet, diltiazem, pravastatin, metoprolol, and clopidogrel. The subject recovered from the event with sequelae of a sternotomy incision and was discharged from the hospital on Study Day 349 (b) (4). The study drug was interrupted from Study Day 333 (b) (4) to Study Day 373 (b) (4). The subject continued in the study on study drug. The subject's medical history includes past tobacco use (cigarettes), sleep apnea, idiopathic edema, gastroesophageal reflux disease, benign prostatic hypertrophy, and osteoarthritis. Concomitant medications included fluticasone, acetaminophen, cetirizine, furosemide, diclofenac, doxazosin, famotidine, fish oil, multivitamin, and finasteride.

Appendix C: Deep vein thrombosis narratives

Subject OB 302/147-038: [PHEN/TPM 15/92 mg] Bilateral pulmonary thromboembolism and DVT of left leg

27 year-old White female with a history of hypothyroidism (controlled on norgestimate/ethinyl estradiol, citalopram, and levothyroxine) was randomized to PHEN/TPM 15/92 mg. On Study Day 85 (b) (4), the subject was admitted to the emergency room with complaints of sudden onset of shortness of breath and a 4-day history of left calf pain. Laboratory testing revealed a fibrin d-dimer of 3.48 mg/L (normal range, 0.0–1.10 mg/L), and a high-resolution spiral computerized tomogram of the chest showed moderately extensive bilateral pulmonary emboli. Venous dopplers of the lower extremities revealed a left calf deep vein thrombosis (DVT). Treatment of the events included Percocet, enoxaparin, and warfarin. The study drug was permanently discontinued and the subject was discharged from the hospital on Study Day 85 (b) (4).

(b) (4). The subject recovered from the events on Study Day 105 (b) (4) and was withdrawn from the study due to the event on Study Day 107 (b) (4).

Subject OB 302/109-042 [PHEN/TPM 3.75/23 mg] Deep vein thrombosis

36-year-old White female was randomized to PHEN/TPM 3.75/23 mg on (b) (4). On Study Day 187 (b) (4) the subject was noted to be pregnant. The last dose of study drug was taken on Study Day 186 (b) (4). The subject was withdrawn from the study on Study Day 188 (b) (4). Approximately, 2 weeks later, the subject presented to an urgent care with complaints of very painful and sore right lower leg. Physical examination revealed pretibial swelling at the right anterior shin, exquisite tenderness with palpation of the entire right lower extremity, a 10×10 cm area of erythema on the medial mid right shin, and a positive Homan's sign. An ultrasound of the right lower leg was performed and revealed extensive deep vein thrombosis (DVT) of the right lower extremity up to the level of the common femoral vein. The subject was subsequently admitted to the hospital for treatment. Treatment of the event included Norco, aspirin, acetaminophen, intravenous fluids, heparin, morphine, and enoxaparin. The subject was discharged from the hospital on (b) (4), and the event was considered resolved on (b) (4). The subject's medical history includes ear pain and sulfa allergy. Concomitant medications included prenatal vitamins, calcium, docusate, nicotine patch, zolpidem, Augmentin, and cephalexin.

Subject OB 303/172-088 [PHEN/TPM 15/92 mg]: deep vein thrombosis left leg

58-year-old White male with a history of obesity randomized to PHEN/TPM 15/92 mg on (b) (4). On Study Day 169 (b) (4), the subject presented to the emergency room with complaints of leg cramping for 2 days and left lower extremity swelling and redness. An ultrasound was performed, which revealed a deep venous thrombosis within the left common femoral, femoral popliteal vein, and posterior tibial vein; and the subject was admitted to the hospital on the same date. Laboratory tests indicated an antithrombin III of 87, prothrombin time of 12.4, and international normalized ratio of 1.13 (normal units and ranges not reported). The subject was discharged from the hospital on Study Day 170 (b) (4). Treatment of the event included Vicodin, enoxaparin, and warfarin. The last dose of study drug was taken on Study Day 168 (b) (4). The subject discontinued from the study due to the event on Study Day 191 (b) (4). The subject recovered from the event on (b) (4). The subject's medical history includes hypertension and deep vein thrombosis. Concomitant medications included simvastatin, amlodipine, and ibuprofen.

Appendix D: Suicide/self injury narratives

Subject OB-303/151-080 [Placebo]: suicidal ideation without intent

A 48-year-old Caucasian female with a history of obesity was randomized to placebo on (b) (4). The subject had ongoing depression and was being treated with antidepressants and had a past history of suicidal ideation. At screening (b) (4), the subject's PHQ-9 total score was 5, with a score of 3 on Question 5, a score of 1 on Questions 3 and 4, and a score of 0 on Question 9. The C-SSRS responses at screening were positive on Question 1 (wish to be dead) and Question 2 (non-specific active

suicidal thoughts) due to historical events. When the subject's son left for college (1998), she experienced suicidal thoughts which were fleeting (lasting just a few seconds) and occurred less than once a week. On Study Day 194 (b) (4), the subject reported having a 1-day episode of suicidal ideation without intent to act. The investigator assessed the event as moderate in severity and related to study drug in the study database. However, based on additional follow-up information collected on the event, which was not part of the database, the investigator assessed the event as unrelated to study drug. The study drug was permanently discontinued on Study Day 195 (b) (4). On Study Day 200 (b) (4), the subject responded "yes" to C-SSRS Question 2 (non-specific active suicidal thoughts). The subject described the event as fleeting thoughts of suicide two to three times a day in the last few weeks with no intent to act. The event was attributed by the subject to disappointment in herself and not being happy with the way her life was going. The PHQ-9 total score on the same day was 6, with a score of 2 on Question 6 and a score of 1 on Questions 1, 2, 4, and Question 9. The subject was referred to a psychiatrist for treatment. The subject had no further episodes of suicidal ideation and felt better. Her husband, an infectious disease physician, had been writing Effexor prescriptions for her since 2007. On Study Day 225 (b) (4), the PHQ-9 total score was 0 (with a 0 on Question 9), and all C-SSRS responses were negative for the remainder of the study. The subject continued in the study off study drug and withdrew consent on Study Day 285 (b) (4). The subject's medical history includes ongoing depression, hypertension, dyslipidemia, stress incontinence, rosacea, sinus headaches, basal cell carcinoma of the right shoulder, tonsillectomy, bilateral breast implants, and seasonal allergies. Concomitant medications included venlafaxine (Effexor) for depression, ipratropium bromide, mometasone furoate, cromolyn, calcium carbonate, aspirin, atenolol, and loratadine.

Subject OB-302/148-017 [PHEN/TPM 3.75/23 mg]: suicidal ideation

A 55-year-old Caucasian female with a history of obesity was randomized to PHEN/TPM 3.75/23 mg on (b) (4). The subject's PHQ-9 total score at screening (b) (4) was 9, with a score of 2 on Questions 1 to 4 ("little interest or pleasure in doing things," "feeling down, depressed, or hopeless," "trouble falling or staying asleep or sleeping too much," and "feeling tired or having little energy" on more than half the days), a score of 1 on Question 6 ("feeling bad about yourself or that you are a failure or have let yourself or your family down" on several days), and a 0 on Question 9 (no suicidal thoughts). The C-SSRS responses at baseline were negative. On Study Day 30, the subject's Cymbalta dose was increased from 30 mg QD to 120 mg QD. On Study Day 33 (b) (4), the subject's PHQ-9 total score was 12, with scores of 2 on Questions 1 to 6 and a score of 0 on Question 9. On Study Day 47 (b) (4), the subject developed suicidal ideation. She commented that she was having problems with her ex-husband following her, trouble with her children, and having problems getting alimony. She wished that she was dead or she could kill herself. She did not have any specific plan for committing suicide but fantasized about being dead because it would be easier. On Study Day 59 (b) (4) the study drug was permanently discontinued. On Study Day 61 (b) (4), the subject recovered from the event and was withdrawn from the study due to the event. At the Early Termination visit on Study Day 61 (b) (4), the subject's PHQ-9 total score was 17, with a score of 2 on Question 9, which indicated that, for more than half

the days, the subject had thoughts that she would be better off dead or of hurting herself in some way. In addition, the subject responded “yes” on C-SSRS Questions 1 and 2 (“wish to be dead” and “suicidal thoughts”). Site personnel had a follow-up phone call with the subject on (b) (4), during which the subject stated that she was doing better. The subject’s medical history includes hypertension, myopia, seasonal allergic rhinitis, obstructive sleep apnea, hernia, hernia repair, gastroesophageal reflux disease, cholecystectomy, bilateral peripheral edema, osteoarthritis of both knees, chronic back pain, bilateral knee pain, bilateral tubal ligation, postmenopausal status, headaches, and depression. Concomitant medications included duloxetine, hydrochlorothiazide, and olmesartan.

Reviewer comment: Subject with history of depression, which worsened within two months of treatment. (PHQ-9 score increased from screening score of 9 or MILD, to 17 or MODERATELY SEVERE two days after discontinuing study drug, and C-SSRS went from negative at baseline to positive on “wish to be dead” and “suicidal thoughts”).

Subject OB-303/127-019 [PHEN/TPM 15/92 mg]: labile emotions

A 66-year-old Caucasian female with a history of obesity was randomized to PHEN/TPM 15/92 mg on (b) (4). At baseline (b) (4), the PHQ-9 score was 5, mostly driven by question 4 (“feeling tired or little energy nearly every day”), but also with positive responses on questions 2 and 5 (0 on question 9). Also on that day, the subject responded “yes” to C-SSRS question 1 commenting “wish to go to sleep and not wake up.” These thoughts occurred with a very low frequency. The PHQ-9 score was 2 on Study Day 17 (b) (4). On Study Day 23 (b) (4), the subject reported an adverse event of labile emotions, and study drug was permanently discontinued on the same day. On Study Day 24 (b) (4), the subject reported an adverse event of a suicidal thought, which resolved without treatment on the same day. On Study Day 25 (b) (4), the adverse event of labile emotions resolved. The subject was withdrawn from the study on Study Day 30 (b) (4), at which time the PHQ-9 score was 14, with positive responses on every question, indicating moderate depression. Also on that day, the subject scored 1 on PHQ-9 question 9 and responded “yes” to C-SSRS question 1 (“wish to be dead”) with the comment, “There was no active suicidal thought about killing herself or any plan. Thought was a 1-day event, easily controlled.” The subject’s medical history includes dyslipidemia, myopia, cataract, mitral valve prolapse, hypothyroidism, cholelithiasis with cholecystectomy, hiatal hernia, irritable bowel syndrome, constipation, diarrhea, appendicitis with appendectomy, hemorrhoids with hemorrhoidectomy, incontinence, bladder repair, hysterectomy, insomnia, migraines, bilateral knee and lumbar back osteoarthritis, fractured left ankle, degenerative disc disease, left and right great toe surgery, depression, and seasonal allergies. Concomitant medications include venlafaxine, levothyroxine, zolpidem tartrate, vitamin B12, simvastatin, and ibuprofen. The investigator considered the event of labile emotions as severe in severity and related to study drug, and the event of suicidal thought as mild in severity and related to study drug.

Subject OB-302/196-035 [PHEN/TPM 15/92 mg]: suicidal ideations

A 53-year-old African female with a history of obesity was randomized to PHEN/TPM 15/92 mg on (b) (4). The study drug was permanently discontinued on Study Day 290 (b) (4) for the non-serious adverse event of “feeling funny.” The subject continued in the study. On Study Day 395 (b) (4), 105 days after discontinuation of study drug, the subject was feeling suicidal due to confusion stemming from frequent hallucinations. The subject, a school bus driver, hallucinated about running people over and about being told to shop by television. The subject’s symptoms were exacerbated by alcohol consumption. The subject was attending Alcoholics Anonymous meetings. The subject reported having feelings of worthlessness or guilt nearly every day with diminished ability to think. The subject was involuntarily hospitalized for evaluation and treatment. Treatment of the event included bupropion and risperidone. The subject recovered from the event on Study Day 400 and was discharged from the hospital. At the final study visit, the subject responded “yes” to C-SSRS question 1 (“wish to be dead”) and question 2 (“non-specific active suicidal thoughts”). The subject stated that she had fleeting thoughts of running into the canal, approximately 2 to 5 times a week, and had some difficulty controlling her thoughts. However, deterrents stopped her from acting on those thoughts. The subject stated that she wanted to end or stop her pain. The subject’s medical history includes cholecystectomy, hernia repair, tubal ligation, and moderate depression (since (b) (4)). Concomitant medications included fluoxetine (Prozac) for depression from (b) (4). The subject’s depression was ongoing at the end of the study and was being treated with bupropion and risperidone. This subject is not included in the TME of Suicidal/self injury because it is not considered treatment emergent.

Appendix E: Cardiac arrhythmia narratives

Subject OB 303/160-109 [PHEN/TPM 7.5/46]: atrial fibrillation

67-year-old White female with a history of obesity was randomized to PHEN/TPM 7.5/46 mg on (b) (4). On Study Day 43, the subject presented to the emergency room and was admitted with complaints of palpitations without chest pain. The subject’s heart rate was reportedly 160 bpm. A rhythm strip showed evidence of atrial fibrillation with rapid ventricular response versus paroxysmal supraventricular tachycardia. After two 10 mg doses of intravenous diltiazem, the subject converted to sinus rhythm. An electrocardiogram showed normal sinus rhythm with occasional premature ventricular complexes and evidence of a right bundle branch block. Additional treatment of the event included aspirin and atenolol. The subject recovered from the event on Study Day 43. The subject was discharged from the hospital on Study Day 44. The study drug was interrupted from Study Day 43 to Study Day 48. The subject continued in the study. The subject’s medical history includes past tobacco use, hypothyroidism, cataracts bilateral eyes, dyslipidemia, ear infection, asthma, varicose veins, hemorrhoids, gastroesophageal reflux disease, osteoarthritis of the neck and shoulder, back pain, frequent headaches, hysterectomy, tubal ligation, recurrent urinary tract infections, basal cell carcinoma of the nose, partial thyroidectomy, keratoses, right breast biopsy (benign), bladder lift, thyroid nodule (benign), Mohs procedure on nose for basal cell carcinoma, and allergy to sulfa. Concomitant medications included probiotic acidophilus, hydrocodone/APAP,

acetaminophen, pantoprazole, aspirin, Fioricet, albuterol, multivitamins, omega 3 fish oil, selenium, antioxidant formula, atorvastatin, calcium, and levothyroxine.

Subject OB 303/196-085 [PHEN/TPM 15/92 mg]: syncope

50-year-old White male with a history of obesity randomized to PHEN/TPM 15/92 mg on (b) (4). On Study Day 04 (b) (4), the subject experienced a syncopal episode while leaving the driveway. The subject was found unconscious in the vehicle with the airbag deployed. The subject was subsequently admitted to the hospital for evaluation and treatment. On that same date, a computerized tomography (CT) scan of the abdomen showed no acute intraabdominal processes; CT scan of the brain revealed no acute intracranial process; chest X-ray revealed no acute cardiopulmonary process; and an electrocardiogram and echocardiogram were reported as normal. On Study Day 05, a carotid duplex ultrasound was performed with no hemodynamically stenosis noted. The subject recovered from the event and was discharged from the hospital on Study Day 06 (b) (4). The study drug was permanently discontinued on Study Day 04 (b) (4). The subject was discontinued from the study due to the event on Study Day 22 (b) (4). The subject's medical history includes current tobacco use (cigarettes), hypertension, dyslipidemia, chronic fatigue, sleep apnea, unstable angina, and removal of pilonidal cysts. Concomitant medications included Robitussin AC, guaifenesin, clopidogrel, metoprolol, Accuretic, and atorvastatin.

Subject OB 302/153-036 [PHEN/TPM 15/92 mg] Atrial fibrillation

59-year-old White male with a history of obesity was randomized to PHEN/TPM 15/92 mg on (b) (4). On Study Day 274, the subject was admitted to the hospital for treatment of a left tibial plafond fracture with associated metatarsal fractures (non-serious adverse events). In a pre-operative holding area, the subject was found to be in atrial fibrillation. Laboratory testing revealed a sodium of 140, potassium of 3.5, chloride of 187, carbon dioxide of 25, blood urea nitrogen of 12, creatinine of 1.0, and glucose of 106 (units and normal ranges not provided). The subject's blood pressure was 144/86 mmHg with a pulse of 118 beats per minute and respirations of 19. An electrocardiogram revealed atrial flutter with variable atrioventricular block. On that same date, transthoracic echocardiogram revealed mildly dilated left ventricle chamber size, mild concentric left ventricular hypertrophy, mildly dilated left atrium, and normal ventricular systolic function. Treatment of the event included diltiazem and fondaparinux (Arixtra- anticoagulant). On an unknown date during the hospitalization, the atrial fibrillation spontaneously converted to normal sinus rhythm. On Study Day 277, the subject recovered from the event and was discharged from the hospital. The study drug was interrupted from Study Day 245 to Study Day 278. The subject's medical history includes hypertension, dyslipidemia, sleep apnea, benign prostatic hypertrophy, erectile dysfunction, depression, benign prostatic hypertrophy, seasonal allergies, and left wrist fracture. Concomitant medications included metoprolol, fluticasone, lisinopril, aspirin, vardenafil, diltiazem, venlafaxine, and citalopram.

Subject OB 303/165-071 [PHEN/TPM 7.5/46 mg]: Tachycardia

40-year-old White female with a history of obesity randomized to PHEN/TPM 7.5/46 mg on (b) (4). On Study Day 324 (b) (4), the subject underwent a dilation and

curettage, hysteroscopy, and removal of uterine polyps. Post-operatively, the subject experienced episodes of tachycardia with a heart rate in the range of 133 to 155 bpm. An electrocardiogram confirmed tachycardia. Cardiac enzymes, thyroid function tests, a computed tomography angiography to rule out pulmonary embolus, a computed tomography of the pelvis to rule out deep vein thrombosis, and an echocardiogram were unremarkable. The subject was started on intravenous verapamil and diltiazem, which resulted in the subject's heart rate converting to normal sinus rhythm with a rate of 40 bpm, increasing to 72 bpm after the medications were stopped. At the time of discharge, the subject was asymptomatic with a controlled heart rate of 60–70 bpm. The subject recovered from the event on Study Day 324 and was discharged from the hospital on Study Day 325. The study drug was interrupted from Study Day 320 to Study Day 335. The subject continued in the study. The subject's medical history includes hypertension, dyslipidemia, gestational diabetes, occasional headaches, seasonal allergic rhinitis, Staphylococcal abscess on posterior neck, bilateral tubal ligation, and metabolic syndrome. Concomitant medication included loratadine.

Appendix F: CSS-specified preferred terms and text-strings for abuse potential assessment

Euphoria-related Terms
<p><u>Preferred Terms</u>: Euphoric Mood, Elevated Mood, Feeling Abnormal, Feeling Drunk, Feeling of Relaxation, Dizziness, Thinking Abnormal, Hallucination (all types)</p> <p><u>Text Strings</u>: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high, high feeling, laughter, mood elevated, elation, cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey, drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged, feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness, dizziness and giddiness, felt giddy, giddiness, light headedness, lightheaded, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy, abnormal thinking, thinking irrational, wandering thoughts, illusions, flashbacks, floating, rush, feeling addicted</p>
Terms Related to Impaired Attention, Psychomotor Event, Cognition and Mood
<p><u>Preferred Terms</u>: Somnolence, Stupor, Depersonalization, Mood Altered, Mood Swings, Emotional Disorder, Emotional Distress, Personality Disorder, Impatience, Abnormal Behavior, Delusional Disorder (all types), Irritability, Amnesia, Memory Impairment, Cognitive Disorder, Disturbance in Attention, Mental Impairment, Drug Tolerance, Drug Withdrawal Syndrome</p> <p><u>Text Strings</u>: groggy, groggy and sluggish, groggy on awakening, mental disturbance, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood alterations, mood instability, emotional lability, emotional distress, abnormal behavior, memory loss, decreased memory, cognition and attention disorders and disturbances, decreased concentration, mental slowing, mental disorders, habituation, substance-related disorder</p>
Dissociative and Psychotic Terms
<p><u>Preferred Terms</u>: Psychotic Disorder, Hostility, Anger Paranoia, Confusional State, Disorientation, Dissociation, Thought Blocking, Muscle Rigidity, Agitation</p> <p><u>Text Strings</u>: psychotic episode, disoriented, confusion, disconnected, derealization, detached, fear symptoms, depersonalization, perceptual disturbance, thinking disturbance, sensation of distance from one's environment, blank stare, noncommunicative, sensory distortions, slurred speech, excitement, increased pain threshold, loss of a sense of personal identity</p>

Appendix G: Hallucination/Euphoria narratives

Subject OB-303 148-066 [Placebo]: Euphoric Feeling

A 45 year old Hispanic/Latino female randomized to placebo reported an adverse event of euphoric feeling which resolved on Day 186. The event of euphoria was an isolated event which did not require any dose reduction, and it did not recur during the study. The subject had her last dose on Study Day 279 due to early termination from the study on Study Day 344 due to the need to for other medical treatment which requires the use of excluded medications.

Subject OB-303 108-046 [PHEN/TPM 7.5/46 mg]: euphoric mood

A 53-year-old Caucasian female with a history of obesity was randomized to PHEN/TPM 7.5/46 mg on (b) (4). On Study Day 38 ((b) (4)), the subject experienced a

euphoric mood. The study drug was permanently discontinued on Study Day 39 (b) (4). The subject recovered from the event on Study Day 57 (b) (4). The subject was withdrawn from the study due to the event on Study Day 64 (b) (4). The subject's medical history includes, asthma, osteoarthritis bilateral knees, anemia, tubal ligation, menorrhagia, postmenopausal status, excision of the 6th toe of the left foot, cyst excision from left foot, fluid in talocalcaneal joints, healing burn of the right hand, severe dental caries, and seasonal allergies. Concomitant medications included albuterol, calcium, Citracal with glucosamine, and naproxen.

Subject OB-302 124-102: [PHEN/TPM 15/92 mg]: visual hallucinations

A 42-year-old Caucasian female with a history of obesity was randomized to PHEN/TPM 15/92 mg on (b) (4). On **Study Day 22** (b) (4), the subject developed **visual hallucinations**. The subject recovered from the event on Study Day 34 (b) (4). The study drug was permanently discontinued on Study Day 42 (b) (4). The subject was withdrawn from the study due to the event on Study Day 57 (b) (4). The subject's medical history includes dyslipidemia, back pain, asthma, wheezing/cough, gallstones, hepatitis B, cholecystectomy, irritable bowel syndrome, external hemorrhoids, depression, decreased sex drive, tonsillectomy, breast reduction, neck pain, and allergy to dye. Concomitant medications included montelukast, beclomethasone, albuterol, and Advair.

Subject OB-302 187-025: [PHEN/TPM 15/92 mg] hallucinations, tingling in extremities, nausea, irritable, and incoordination

A 24-year-old Caucasian female with a history of obesity was randomized to PHEN/TPM 15/92 mg on (b) (4). On **Study Day 18** (b) (4), the subject developed **hallucinations**, tingling in extremities, nausea, irritability, and incoordination. The study drug was permanently discontinued on Study Day 22 (b) (4). The subject recovered from the events on Study Day 25 (b) (4). The subject was considered lost to follow-up on Study Day 157 (b) (4). The subject's medical history includes myopia, chronic bronchitis, asthma, gastroesophageal reflux disease, irritable bowel syndrome, gallstones, crepitus, osteoarthritis, anxiety, depression, and cholecystectomy. Concomitant medications included Ortho Tri-Cyclen, hyoscyamine, and escitalopram. .

Subject OB-303 128-026 [PHEN/TPM 15/92 mg]: hallucination

A 60-year-old Caucasian male was randomized to PHEN/TPM 15/92 mg. After 2 weeks into titration **on Study Day 14**, subject reported an adverse event of hallucination which lasted less than 24 hours and was assessed as mild and related to study drug. Subject described that he felt like God was talking to him and encouraging him to spread "The Word". On that same day, subject took meperidine hcl and promethazine for migraine (ongoing medical history since 1993), and also reported mild loss of concentration, moderate anxiety, moderate insomnia, and mild peripheral bilateral hands neuropathy, all of which were assessed as related to study drug. Starting on Study Day 32 subject was started on a reduced dose of study drug until Study Day 56) because of the events of mild concentration and moderate insomnia. The event of hallucination was an isolated event that resolved on the same day it started and did not recur during the remainder of the

subject's study participation. The subject completed the study on study drug. Concomitant medications include amlodipine, benazepril, lexapro for AE of mild situational depression medrol dose pak, meperidine hcl, promethazine hcl for migraines, and sotalol.

Subject OB-303 148-130 [PHEN/TPM 15/92 mg]: visual and auditory hallucination

A 42-year-old Black female randomized to PHEN/TPM 15/92 mg reported on study day 135 auditory and visual hallucinations that were moderate in severity. On Study Day 137 the subject experienced severe mood swings, moderate poor emotional control, moderate worsening anxiety, and moderate overreacting, situational, emotional disturbances that were all assessed as related to study drug. The subject started seeing a psychiatrist and with counseling and medication her anxiety improved and resolved on Study Day 140. The subject was diagnosed with moderate bipolar disorder and study drug was permanently discontinued on Study Day 141. After stopping study drug, symptoms improved but at early termination visit, subject mentioned the hallucinations were still ongoing. The subject's medical history includes ongoing anxiety since 2000, hypertension, myopia, conjunctivitis, iron deficiency anemia, hysterectomy, uterine fibroids, transient ischemic attack, and allergies to shellfish and penicillin. The subject's mother had a history of schizophrenia. Concomitant medications include ziprasidone hydrochloride, divalproex sodium, acetazol HC, escitalopram for anxiety as identified in subject history, ciprofloxacin, lisinopril, Darvocet-N 100, tobramycin 0.3%, Dyazide, amlodipine, and multivitamin.

Subject OB-303 194-039 [PHEN/TPM 15/92 mg]: auditory hallucination

A 70-year-old Caucasian female randomized to PHEN/TPM 15/92 mg experienced mild auditory hallucinations on **Study Day 78**. The subject described the event as hearing sounds like background voices from a crowd usually in the morning when tired. Initially the subject would experience the auditory hallucinations 2-3 times a week, but frequency of episodes improved to 2-3 times a month. The event did not interrupt the subject's daily activity and the subject continued in study at the same dose. The auditory hallucinations resolved on Study Day 271. On Study Day 391, the subject completed study on study drug. Concomitant medications included vitamin D3, vitamin B-12, and hydrochlorothiazide.

Subject OB-303 145-040 [PHEN/TPM 15/92 mg]: Euphoria

A 55-year-old Caucasian female randomized to PHEN/TPM 15/92 mg after 1 week into titration on Study Day 9 reported an adverse event of euphoria which resolved next day. Subject reported no other side effects during this period. The event of euphoria was an isolated event which did not require any dose reduction, and it did not recur during the study period. Concomitant medications included Ibuprofen, multivitamin, sertraline (for menopause), and Vitamin-D.

Subject OB-202 0545 [Phen 15/Tpm 100]: Euphoria

A 55-year-old White female, with a history of obesity and Type 2 diabetes, was Phentermine and Topiramate [15/100 mg]. On the first day of dosing, the subject reported an adverse event of euphoria. This event did not require any dose reduction or

concomitant medication. The event remained ongoing at the end of study OB-202 and continued with the same severity with no action taken when subject rolled over to the long term studies, DM-230 and subsequently into DM-231. The event was finally resolved on Study Day 535. Concomitant medications during study OB-202 include metformin, glyburide, hydrochlorothiazide, and ferrous sulfate.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 22-580/N-000

Drug Name: QNEXA[®] Controlled Release Capsules (a combination of immediate-release phentermine hydrochloride beads and modified-release topiramate beads formulated for oral administration)

Indication(s): Treatment of obesity, including weight loss and maintenance of weight loss, in conjunction with diet and exercise.

Applicant: Vivus

Date(s): Submitted December 29, 2009

Review Priority: Standard

Biometrics Division: Division of Biometrics 2 (HFD-715)

Statistical Reviewer: Lee-Ping Pian, Ph.D.

Concurring Reviewers: Todd Sahlroot, Ph.D., Deputy Director
Tom Permutt, Ph.D., Director

Medical Division: Division of Metabolic and Endocrine Products (HFD-510)

Clinical Team: Mary Roberts, M.D., Medical Reviewer
Eric Colman, M.D., Deputy Director

Project Manager: Pat Madara, Pooja Dharia

1. Summary

Qnexa, a fixed-dose combination of phentermine hydrochloride (PHEN) and topiramate (TPM), was shown to be efficacious in reducing body weight for 2 of the 3 doses studied, PHEN/TPM 15/92 mg and PHEN/TPM 7.5/46 mg. The evidence for efficacy comes from factorial Study OB-301 which compared each combination dose to the respective components at the same dose and to placebo. This trial, by virtue of its design, was capable of providing evidence of efficacy in support of the combination drug rule which is the standard for evaluating efficacy in combination products. Results showed that all comparisons of the combinations to their components were statistically significant for the two co-primary efficacy endpoints, percentage change in weight from baseline and the proportion of patients with a minimum 5% weight loss from baseline. The combinations provided an additional 3 to 5 kg average reduction in body weight compared to weight changes seen in the monotherapy arms.

Studies OB-302 and OB-303 both compared two dose combinations to placebo. The combination doses tested in OB-302 and OB-303 were PHEN/TPM 15/92 and PHEN/TPM 3.75/23, and PHEN/TPM 15/92 and PHEN/TPM 7.5/46, respectively. All combinations provided statistically significant weight changes compared to placebo. However, these trials did not have monotherapy arms and therefore could not provide additional evidence of the efficacy of the combination doses in support of the combination drug rule. In particular, PHEN/TPM 3.75/23 mg was tested in study (OB-302) only, not Study OB-301. Therefore, the efficacy of 3.75/23 mg could not be confirmed from the data provided.

Discontinuations due to adverse events were dose related. Psychiatric and nervous system disorders resulted in the greatest number of discontinuations across all 3 studies. Only the 15/92 mg dose was significantly different from placebo in the frequency of discontinuations due to these disorders (Table 5).

2. Background

Phentermine hydrochloride up to 37.5 mg is indicated for short-term (a few weeks) weight reduction. Topiramate 200-400 mg/day (2 divided doses) is indicated for treatment of epilepsy and migraine headache prophylaxis.

Qnexa is a fixed combination drug product for weight loss. Qnexa is comprised of immediate-release phentermine hydrochloride beads (PHEN) and modified-release topiramate beads (TPM).

After randomization, weekly titration started with the lowest dose of the 4 proposed dose strengths PHEN/TPM, 3.75/23 mg. The three higher doses are PHEN/TPM 7.5/46 mg (mid dose), PHEN/TPM 11.25/69 mg (three-quarter dose), and PHEN/TPM 15/92 mg (full dose). The PHEN/TPM 11.25/69 mg was intended only as a titration dose.

3. Results

The phase 3 studies were all randomized, double-blind, multicenter, parallel-group, and placebo-controlled.

OB-301 was a factorial study which compared full-dose (PHEN/TPM 15/92 mg) and mid-dose (PHEN/TPM 7.5/46 mg) Qnexa with placebo and the respective PHEN and TPM components after 28 weeks of treatment.

The PHEN/TPM 3.75/23 mg dose was not studied against its components in study 301. The dose was only studied in OB-302 which compared full-dose (PHEN/TPM 15/92 mg) and low-dose (PHEN/TPM 3.75/23 mg) with placebo after 56 weeks of treatment. The treatment groups in OB-303 were PHEN/TPM 15/92 mg and PHEN/TPM 7.5/46 mg Qnexa and placebo.

Table 1 presents summary of the 3 studies.

Table 1 Phase 3 study summary

	OB-301	OB-302	OB-303
Study location (# sites)	USA (34)	USA (91)	USA (93)
dates	12/03/2007 – 9/30/2008	11/01/2007 – 5/19/2009	11/01/2007 – 6/30/2009
study duration	screening: 2 weeks titration: 4 weeks treatment: 24 weeks	screening: 2 weeks titration: 4 weeks treatment: 52 weeks	screening: 2 weeks titration: 4 weeks treatment: 52 weeks
study population	adults \leq 70 years of age BMI: \geq 30 kg/m ² & \leq 45kg/m ² No diabetics	adults \leq 70 years of age BMI: \geq 35 kg/m ² No diabetics	adults \leq 70 years of age BMI \geq 27 kg/m ² & \leq 45kg/m ² \geq 2 obesity-related co-morbid conditions
Treatment groups	total n=756 1:1:1:1:1:1 stratified by gender Placebo (n=109) PHEN 7.5 mg (109) PHEN 15 mg (108) TPM 46 mg (108) TPM 92 mg (107) PHEN/TPM 7.5/46 mg (107) PHEN/TPM 15/92 mg (108)	n=1267 2:1:2 stratified by gender (male \geq 20%) Placebo (514) PHEN/TPM 3.75/23 mg (241) PHEN/TPM 15/92 mg (512)	n=2487 2:1:2 stratified by gender (male \geq 20%) and diabetes status Placebo (994) PHEN/TPM 7.5/46 mg (498) PHEN/TPM 15/92 mg (995)
Study objective	Combination superior to placebo and components	Combination superior to placebo	Combination superior to placebo
co-primary endpoints	Percent weight loss at Week 28 with LOCF; and Percentage of patients with \geq 5% weight loss at week 28 with LOCF	Percent weight loss at Week 56; and Percentage of patients with at least 5% weight loss at Week 56	Percent weight loss at Week 56; and Percentage of patients with at least 5% weight loss at Week 56
Secondary endpoints	Percentage of patients with \geq 10% weight loss at Week 28 with LOCF, Change in waist circumference from baseline to Week 28 with LOCF Changes in IWQOL*-Lite	Absolute weight loss at Week 56 Percentage of patients with \geq 10% weight loss at Week 56 and Change in waist circumference from	Absolute weight loss at Week 56 Percentage of patients with \geq 10% weight loss at Week 56 and Change in waist circumference from

	OB-301	OB-302	OB-303
	composite and individual domain scores at Week 28 with LOCF	baseline to Week 56	baseline to Week 56

*IWQOL=Impact of Weight on Quality of Life

Patient disposition

The analysis of patient disposition was based on the set of randomized patients (100%). The safety population was defined as all randomized patients who received at least one dose of study drug. The sponsor's ITT population was defined as all randomized patients who took at least one dose of the study drug, had a baseline and at least one post-baseline measurement of body weight (regardless of receiving study drug or being off study drug). The modified ITT population (MITT) was defined as all ITT patients who had at least one post baseline measurement of body weight within 7 days of the last dose of study drug. The MITT was smaller than the ITT population by approximately 2% for all 3 studies. Tables 2-4 summarize the disposition of patients for the 3 studies, respectively.

Approximately 66% of patients in Study 301 completed the 28-week study on drug. The 56-week completion rates for studies 302 and 303 were 54% and 62%, respectively.

Table 2 Patient disposition – Study 301

	Placebo (N=109)	PHEN 7.5 (N=109)	TPM 46 (N=108)	PHTN/TPM 7.5/46 (N=107)	PHEN 15 (N=108)	TPM 92 (N=107)	PHTN/TPM 15/92 (N=108)	Total (N=756)
n(%)								
Safety	109	109	106 (98)	106 (99)	108	107	108	753
ITT	103 (95)	104 (95)	102 (94)	103 (96)	106 (98)	105 (98)	103 (95)	726 (96)
MITT*	102 (94)	100 (92)	100 (93)	98 (92)	105 (97)	104 (97)	101 (94)	710 (94)
Completed visits	74 (68)	79 (73)	78 (72)	78 (73)	80 (74)	77 (72)	75 (69)	541 (72)
Completed*	69 (63)	74 (68)	72 (67)	73 (68)	72 (67)	67 (63)	68 (63)	495 (66)
Discontinued	40 (37)	35 (32)	36 (33)	34 (32)	36 (33)	40 (37)	40 (37)	261 (35)
AE	8 (7)	10 (9)	8 (7)	16 (15)	11 (10)	18 (17)	23 (21)	94 (12)
Lost follow-up	12 (11)	13 (12)	11 (10)	6 (6)	7 (7)	8 (9)	9 (8)	66 (9)
Consent withdrew	9 (8)	7 (6)	6 (6)	4 (4)	8 (7)	5 (5)	3 (3)	42 (6)

*receiving study drug

Table 3 Patient disposition – Study 302

	Placebo	PHEN/TPM	PHEN/TPM	Total
n(%)		PHEN/TPM 3.75/23	PHEN/TPM 15/92	
Randomized	514	241	512	1267
Safety	513	240	511	1264
ITT	498 (97)	234 (97)	498 (97)	1230 (97)
MITT	485 (94)	229 (95)	487 (95)	1201 (95)
Completed all study visits	272 (53)	147 (61)	340 (66)	759 (60)
Completed all visits on study drug	241 (47)	138 (57)	301 (59)	680 (54)
Discontinued study drug	272 (53)	102 (42)	210 (41)	584 (46)
Adverse event	43 (8)	28 (12)	83 (16)	154 (12)
Subject lost to follow-up	89 (17)	27 (11)	53 (10)	169 (13)
Subject withdrew consent	86 (17)	28 (12)	39 (8)	153 (12)
Lack of efficacy	23 (4.5)	6 (2.5)	6 (1.2)	35 (2.8)

Table 4 Patient disposition – Study 303

	Placebo	PHTN/TPM	PHTN/TPM	Total
n(%)		7.5/46	15/92	
Randomized	994	498	995	2487
Safety Set	993	498	994	2485
Intent-to-Treat Set	979 (99)	488 (98)	981 (99)	2448 (98)
Modified Intent-to-Treat Set	957 (96)	482 (97)	963 (97)	2402 (97)
Completed all study visits	616 (62)	374 (75)	733 (74)	1723 (69)
Completed all visits on study drug	564 (57)	344 (69)	634 (64)	1542 (62)
Discontinued study drug	429 (43)	154 (31)	360 (36)	943 (38)
Adverse event	89 (9)	58 (12)	192 (19)	339 (14)
Subject withdrew consent	139 (14)	34 (7)	69 (7)	242 (10)
Subject lost to follow-up	126 (13)	41 (8)	62 (6)	229 (9)
Lack of efficacy	39 (3.9)	3 (0.6)	5 (0.5)	47 (1.9)

Figure 1 displays Kaplan Meire curves for time to study drug discontinuation by treatment groups in the randomized population. Figure 2 displays time to discontinuation of study drug if the reason for discontinuation was due to adverse events. The 2 most frequent adverse events prompting discontinuation of study medication were psychiatric and nervous system disorders, both of which were dose related.

The Cochran Armitage trend test for dose response stratified by study was significant ($p < 0.001$) for both types of adverse events. Table 6 displays the common odds ratio (95% CI) and p-value for each dose versus placebo. The PHEN/TPM 15/92 mg dose was significantly worse than placebo in AE discontinuation from the study drug. The other 2 doses were not significantly different from placebo which applies to both AEs.

Figure 1 Time to discontinuation of study drug

RAND
1

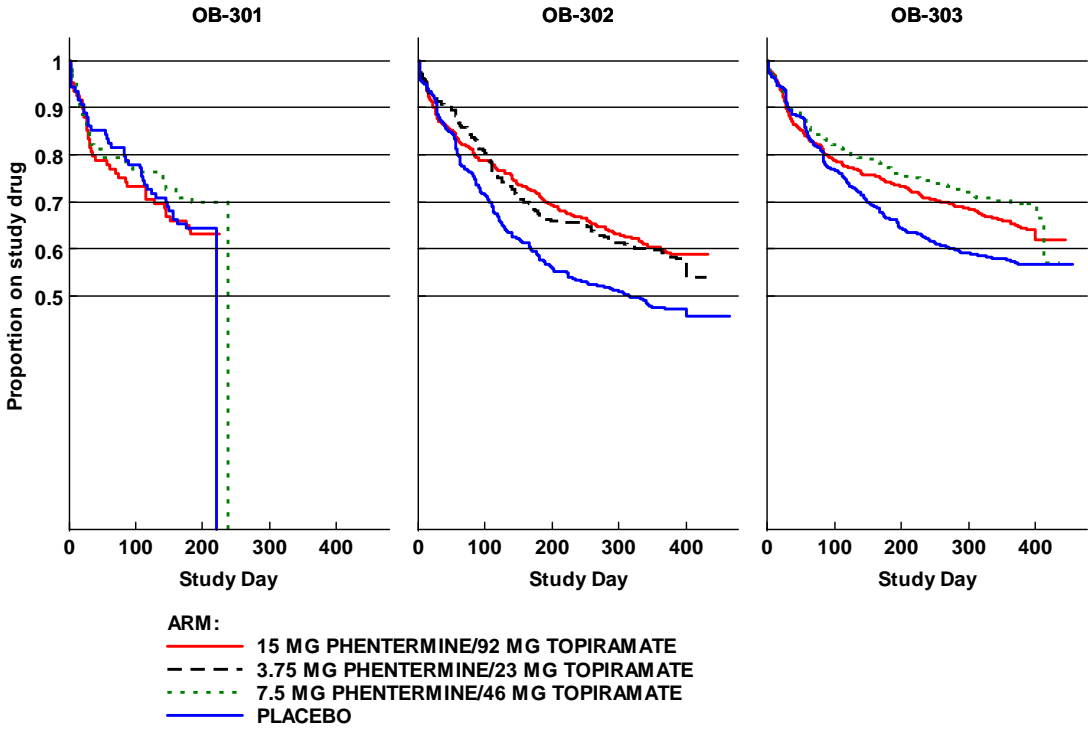


Figure 2 Time to discontinuation of study drug for any AE

RAND
1

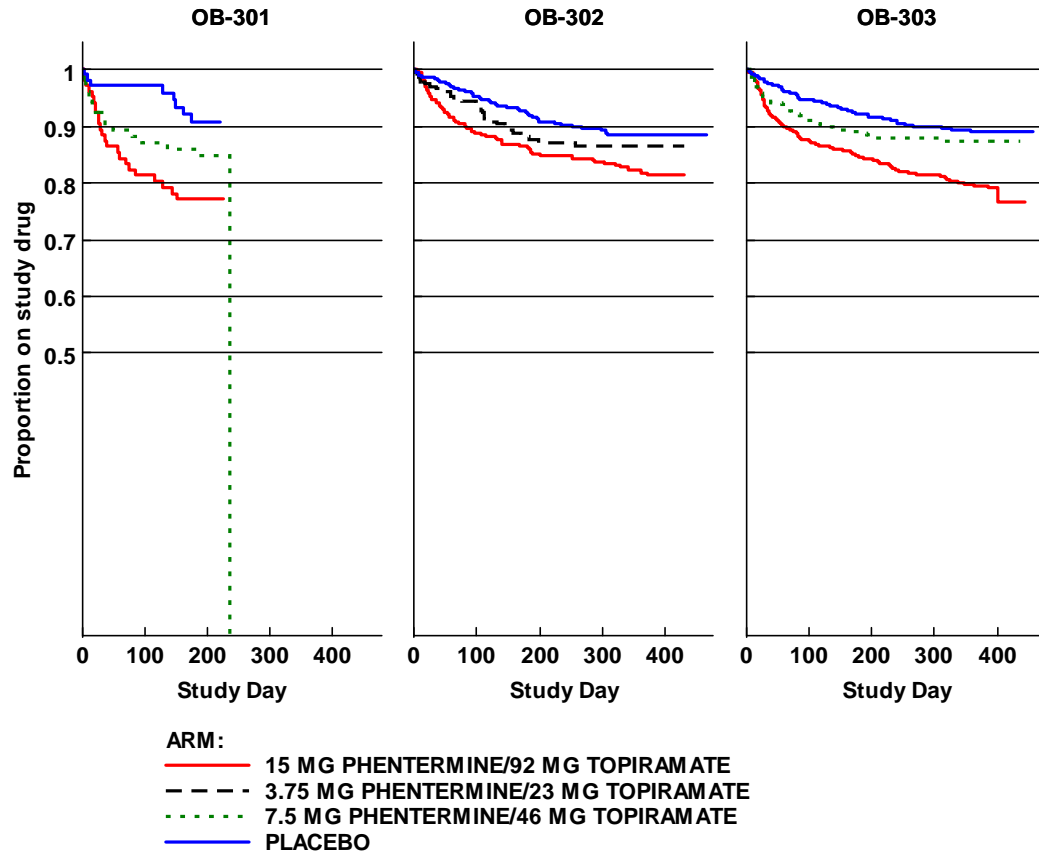


Table 5 Analyses of discontinuation of study drug due to psychiatric and nervous system AE – all randomized patients

	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
301	n=109		n=107	n=108
302	n=514	n=241		n=512
303	n=994		n=498	n=995
Psychiatric				
301	1 (0.9%)		2 (1.9%)	6 (5.6%)
302	4 (0.8%)	6 (2.5%)		22 (4.3%)
303	14 (1.4%)		11 (2.2%)	46 (4.6%)
Stratified by study				
OR vs. placebo				
[95% CI],				
2-sided p-value				
		3.3 [0.8, 15.8]	1.6 [0.7, 3.7]	4 [2.4, 7.1]
		p=0.08	p=0.23	p<0.001
Nervous system				
301	1 (0.9%)		3 (2.8%)	9 (8.3%)
302	10 (2%)	3 (1.2%)		15 (2.9%)

	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
303	13 (1.3%)		10 (2%)	44 (4.4%)
stratified by study				
OR vs. placebo				
[95% CI],		0.6 [0.1, 2.5]	1.7 [0.8, 3.9]	2.9 [1.8, 4.9]
2-sided p-value		p=0.57	p=0.22	p<0.001

OR=odds ratio

Figure 3 Time to discontinuation of study drug due to psychiatric disorder

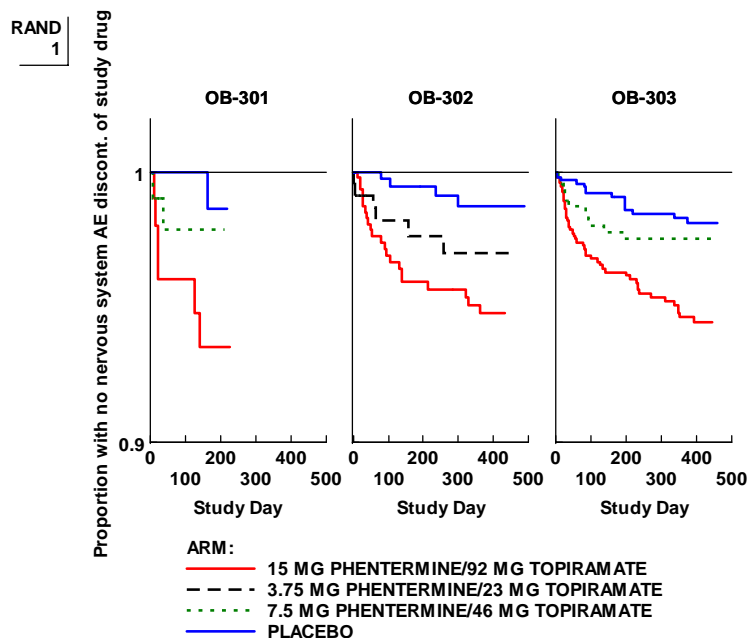
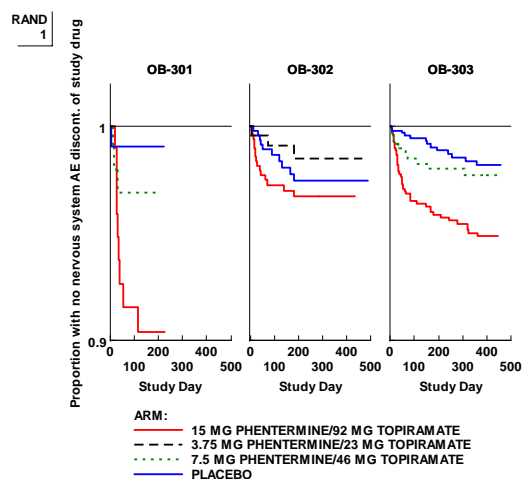


Figure 4 Time to discontinuation of study drug due to nervous system AE



Demographics and baseline characteristics:

Table 6 summarizes baseline and demographic characteristics by study for all randomized patients. Mean age were 46, 43, and 51 years for studies 301, 302 and 303, respectively. The majority of patients were females and Caucasian. Average weight was a little over 100 kg for studies 301 and 303 and 116 kg for study 302. The BMI were 36 kg/m², 37 kg/m² for studies 301 and 303 and 42 kg/m² for study 302 (inclusion criteria BMI \geq 35 kg/m² for study 302 and BMI \geq 30 kg/m² and BMI \leq 45 kg/m² for studies 301 and 303).

Table 6 Demographics and baseline characteristics by study*

	Study 301 n=756	Study 302 n=1267	Study 303 n=2487
Age (years)			
Mean (SD) [min, max]	46 (11.9) [18, 71]	43 (11.8) [18, 70]	51 (10.4) [19, 71]
Gender n (%)			
Female	599 (79%)	1050 (83%)	1737 (70%)
Race %			
Caucasian	79%	79%	86%
African	19%	18%	12%
Other	2%	3%	2%
Weight (kg)			
Mean (SD) [min, max]	101 (15.5) [65, 167]	116 (21.2) [71, 217]	103 (17.9) [58, 163]
Height (cm)			
Mean (SD) [min, max]	167 (8.6) [145, 199]	166 (8.8) [132, 201]	168 (9.7) [127, 201]
Body mass index (kg/m ²)			
Mean (SD) [min, max]	36 (4.1) [30, 45]	42 (6.2) [34, 79]	37 (4.5) [21, 51]
Waist circumference (cm)			
Mean (SD) [min, max]	111 (11.1) [85, 157]	121 (14.4) [88, 198]	113 (12.3) [80, 157]
SBP (mmHg)			
Mean (SD) [min, max]	122 (13) [82, 163]	122 (11) [84, 166]	128 (14) [73, 188]
DBP (mmHg)			
Mean (SD) [min, max]	79 (9) [26, 100]	77 (8) [51, 100]	81 (9) [50, 120]
HR (bpm)			
Mean (SD) [min, max]	73 (10) [45, 114]	73 (9) [46, 108]	72 (10) [40, 111]

Other baseline characteristics by study

	Study 301 (n=726)	Study 302 (n=1267)	Study 303 (n=2487)
LDL cholesterol (mg/dL)			
Mean (SD) [min, max]	126 (32) [46, 291]	121 (31) [30, 271]	123 (35) [8, 292]
HDL cholesterol (mg/dL)			
Mean (SD) [min, max]	52 (15) [17, 138]	50 (12) [23, 112]	49 (14) [8, 138]
Total cholesterol (mg/dL)			
Mean (SD) [min, max]	205 (36) [110, 405]	194 (35) [85, 363]	204 (40) [78, 395]
Triglycerides (mg/dL)			
Mean (SD) [min, max]	135 (65) [31, 467]	116 (39) [33, 262]	162 (74) [33, 656]

	Study 301 (n=726)	Study 302 (n=1267)	Study 303 (n=2487)
Fasting serum glucose (mg/dL)	94 (10) [62, 125]	93 (9) [42, 141]	106 (22) [43, 295]
Mean (SD) [min, max]			
HbA _{1c}			2478
Mean (SD) [min, max]	5.5 (0.4) [4, 6.9]		5.9 (0.8) [4.1, 11.9]

*n might vary by baseline characteristics

Statistical Analysis

In study OB-301, the confirmation of efficacy for the combination was based on a set of three pair-wise comparisons (i.e., combination versus each components and combination versus placebo). All three pairwise comparisons must reach the 5% significance level for both of the co-primary endpoints in order for that dose to be considered effective according to the “combination rule”.

The multiple comparison issue posed by two combination doses was addressed by a step-down procedure which tested the high dose PHEN/TPM 15/92 mg first and, if significant, then tested the second combination dose.

The primary objective of Studies 302 and 303 was to demonstrate the superiority of the studied combination to placebo on the co-primary efficacy endpoints. These studies did not have monotherapy arms using doses corresponding to the doses in the combination drug arms. Therefore, due to the limitations in the study designs, these trials cannot address the efficacy requirements of the combination rule which is necessary for the efficacy evaluation of combination products.

Body weight percent change from baseline:

The sponsor’s primary efficacy analysis used the ITT population which included both on-drug and off-drug patients. This reviewer used the MITT population which included data only from patients who were on study drug at the time of measurement. The percent weight changes in the 2 populations were very similar with approximately 0.3% more reduction in the on drug patients (MITT). Tables 7-9 display the analysis of covariance results for the 3 respective studies. Figures 5 and 6 display the cumulative distribution and box plot for % weight change from baseline to week 56 in the MITT (LOCF) population.

Table 7 ANCOVA results of mean percent change from baseline – MITT LOCF Week 28 – Study 301

LSM at baseline and % Wt change from baseline				Between treatment difference in % Wt change from baseline		
Trt	n	Baseline (kg) (SE)	% Change (SE)	combo vs. placebo or component	LSM difference (CI)	p- value
15P/ 92T	101	104 (1.4)	-9.5 (0.6)	15P/92T vs. Plb	-7.8 [-9.4, -6.1]	<0.01

15P	105	107 (1.4)	-6.1 (0.6)	15P/92T vs. 15P	-3.5 [-5.1, -1.9]	<0.01
92T	104	110 (.14)	-6.6 (0.6)	15P/92T vs. 92T	-2.9 [-4.6, -1.3]	<0.01
7.5P/ 46T	98	108 (1.4)	-8.9 (0.6)	7.5P/46T vs. Plb	-7.1 [-8.8, -5.5]	<0.01
7.5P	100	106 (1.4)	-5.7 (0.6)	7.5P/46T vs. 7.5P	-3.2 [-4.9, -1.6]	<0.01
46T	100	105 (1.4)	-5.3 (0.6)	7.5P/46T vs. 46T	-3.7 [-5.3, -2.0]	<0.01
Plb	102	105 (1.4)	-1.8 (0.6)			

*ANCOVA model: fixed effects of treatment and gender and baseline weight as a covariate

Table 8 ANCOVA results of mean percent change from baseline – MITT, LOCF Week 56 – Study 302

Treatment	n	LSM	SE	Treatment difference	LSM (SE) 95% CI	p
15 PHEN/92 TPM	487	-11.5	(0.4)	PHEN/TPM 15/92 vs. Placebo	-9.9 (0.5) [-10.8, -9.0]	<0.001
3.75 PHEN/23 TPM	229	-5.3	(0.5)	PHEN/TPM 3.75/23 vs. Placebo	-3.8 (0.6) [-4.9, -2.6]	<0.001
PLACEBO	485	-1.6	(0.4)	PHEN/TPM 15/92 vs. PHEN/TPM 3.75/23	-6.1 (0.6) [-7.3, -5.0]	<0.001

Table 9 ANCOVA results of mean percent change from baseline – MITT, LOCF Week 56 – Study 303

Treatment	n	LSM	SE	Treatment difference	LSM (SE) 95% CI	p
15 PHEN/92 TPM	963	-10.4	(0.2)	PHEN/TPM 15/92 vs. Placebo	-8.6 (0.3) [-9.3, -7.9]	<0.001
7.5 PHEN/46 TPM	482	-8.3	(0.3)	PHEN/TPM 7.5/46 vs. Placebo	-6.5 (0.4) [-7.3, -5.6]	<0.001
PLACEBO	957	-1.8	(0.2)	PHEN/TPM 15/92 vs. PHEN/TPM 7.5/46	-2.1 (0.4) [-2.9, -1.3]	<0.001

Figure 5 Cumulative distribution and box plot of % weight loss – MITT, LOCF

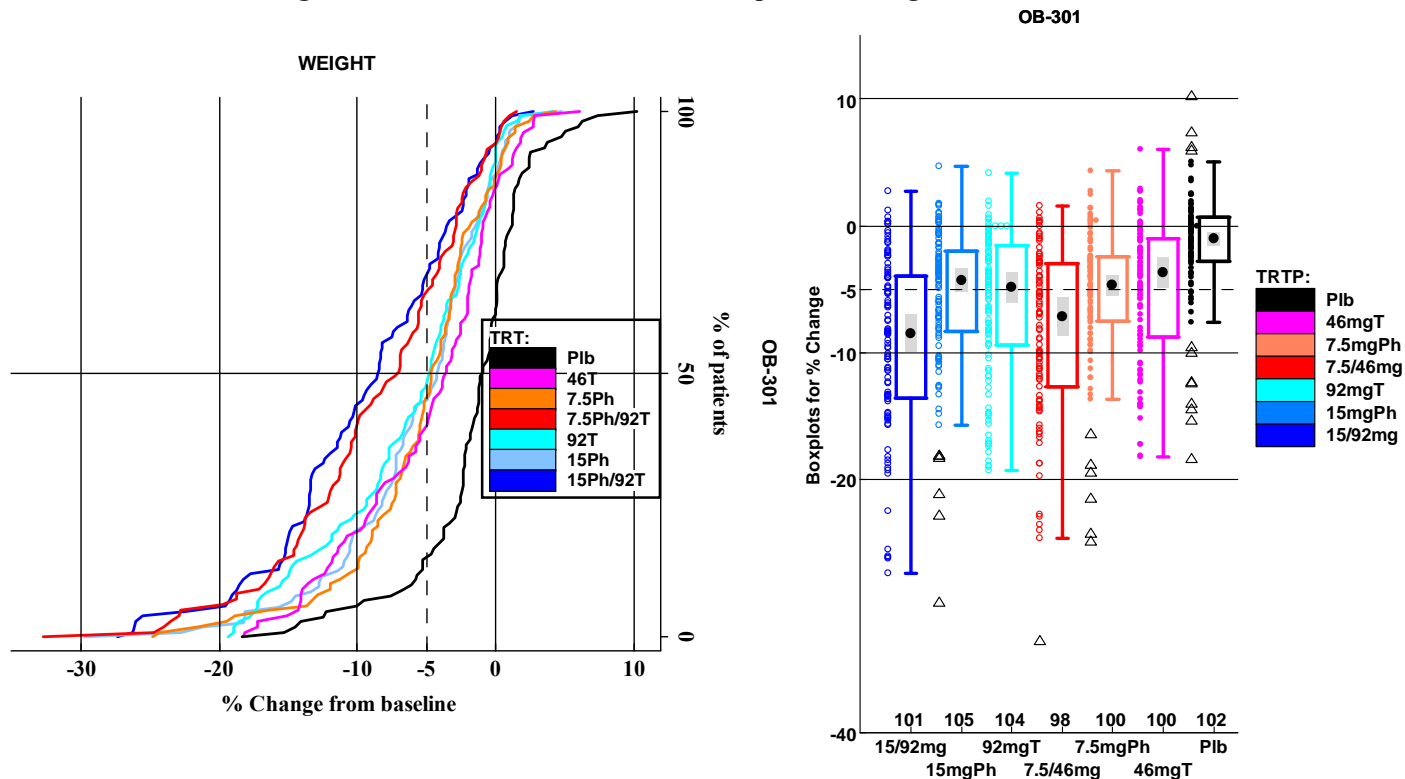


Figure 6 Box plot and cumulative distribution of % weight change from baseline to week 56
Studies 302, 303 – MITT, LOCF

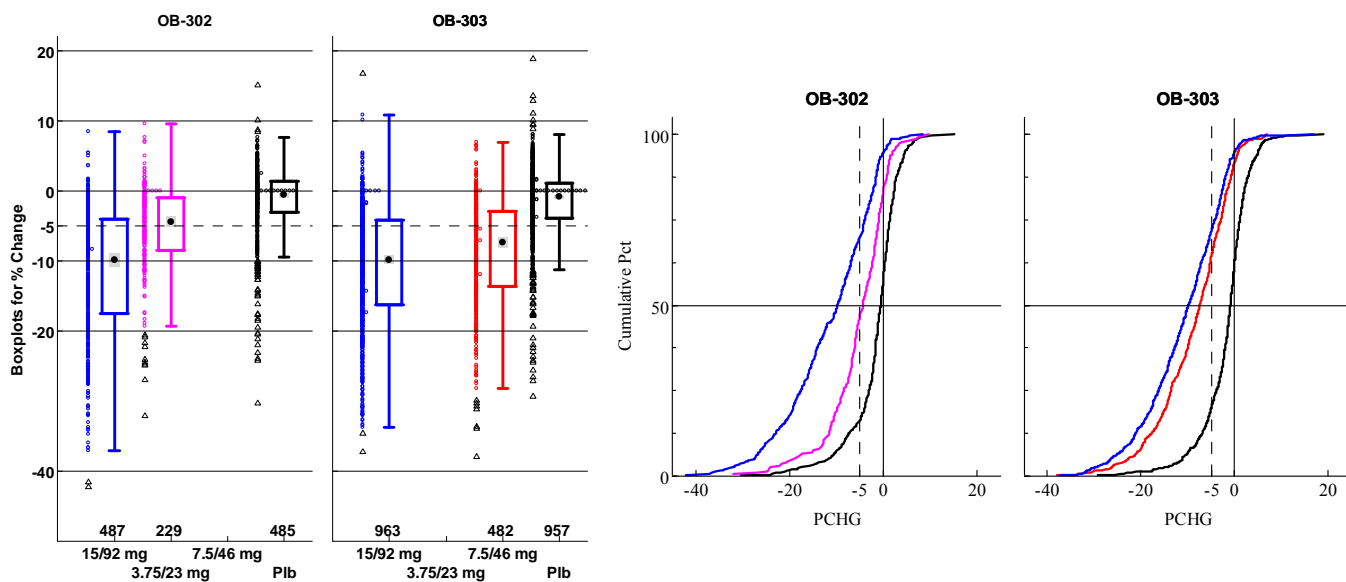


Figure 7 LSM treatment differences of combinations vs. components and placebo in % Weight change from baseline to Week 28 – MITT (patients on drug), LOCF Study 301

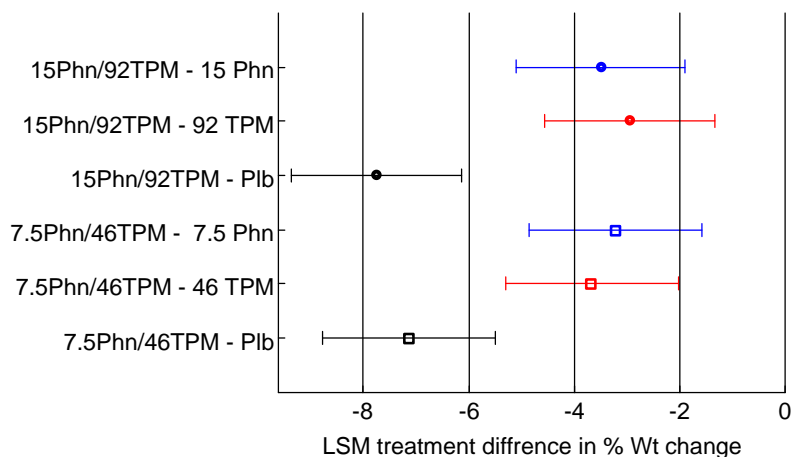


Figure 8 LSM treatment differences in % Weight change from baseline to Week 56 – MITT (patients on study drug), LOCF

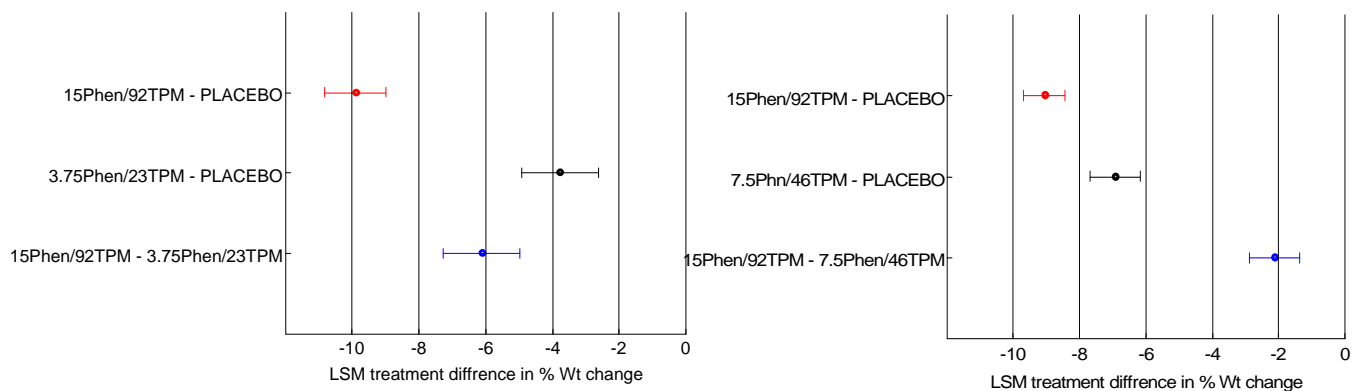
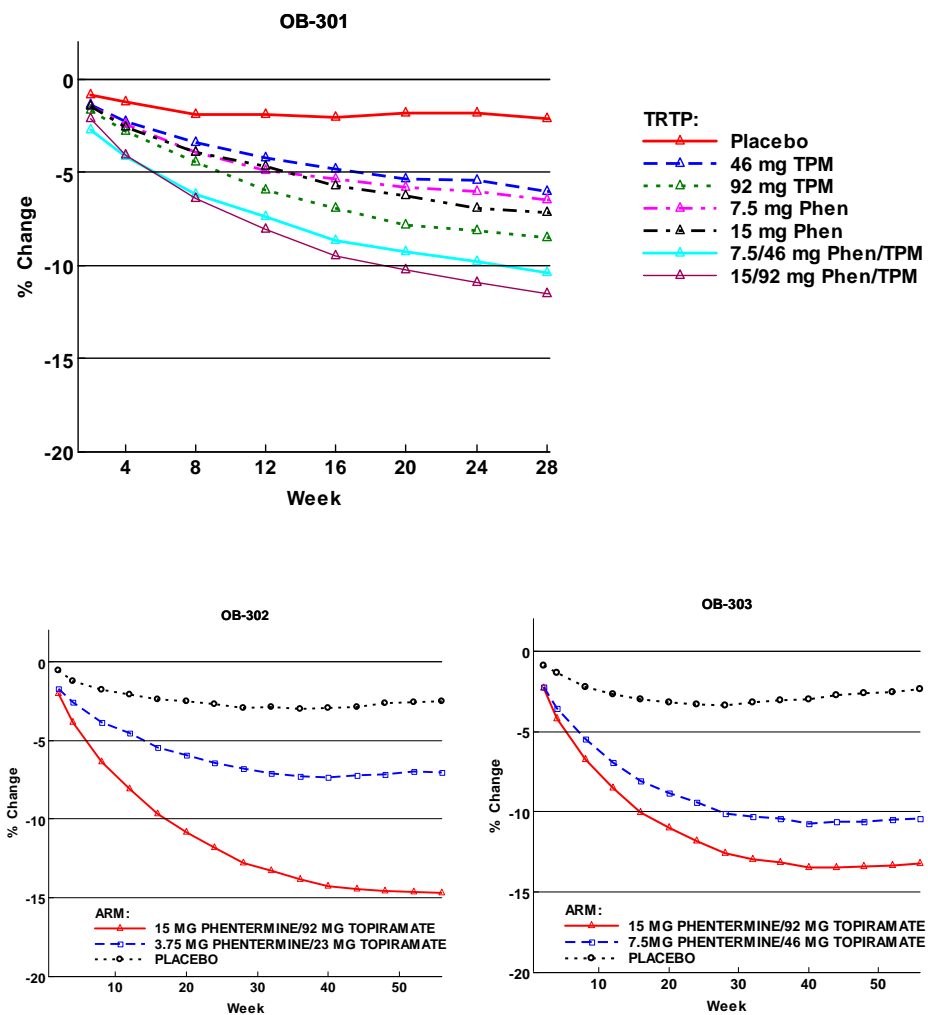


Figure 9 Mean % weight change from baseline by time and treatment group – Patients who completed all visits on study drug



Percentage of patients with $\geq 5\%$ weight loss from baseline (Co-primary endpoint)

Table 10 displays statistical analyses of the percentage of patients with $\geq 5\%$ weight loss from baseline. All comparisons between the combinations and placebo were statistically significant ($p < 0.01$) as well as the combinations vs. the respective components.

Table 10 Risk differences compared to placebo [95% CI] for the percentage of patients with $\geq 5\%$ weight loss from baseline

% of responders	placebo	PHEN/TPM 3.75/23 mg	PHEN/TPM 7.5/46 mg	PHEN/TPM 15/92 mg
301	16%		62%	66%
302	16%	48%		70%
303	20%		64%	72%
vs. placebo				
301			47% [35, 58]	53% [49, 57]
302		31% [24, 39]		54% [48, 59]
303			44% [40, 49]	52% [48, 56]

Combination Study 301	PHEN/TPM 7.5/46 mg	PHEN 7.5 mg	TPM 46 mg	PHEN/TPM 15/96 mg	PHEN 15 mg	TPM 92 mg
% of responders	62%	43%	39%	66%	46%	49%
vs. component		19% [6, 32]	23% [10, 36]		20% [7, 33]	17% [4, 31]

Figure 10 Percentage of patients with $\geq 5\%$ weight loss at Week 28 – MITT, LOCF Study 301

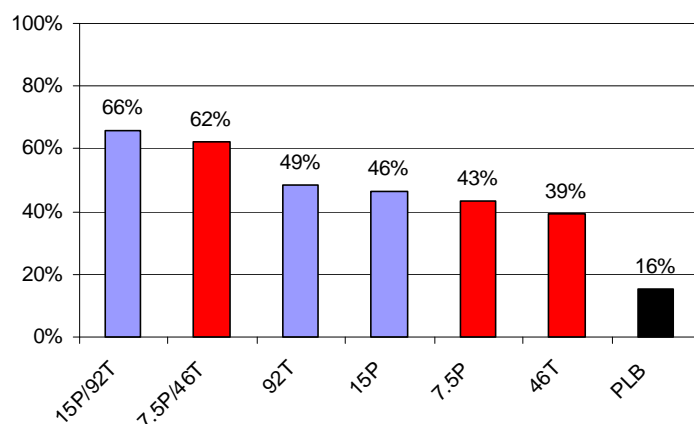


Figure 11 Percentage of patients with $\geq 5\%$ weight loss at Week 56 – MITT, LOCF Study 302

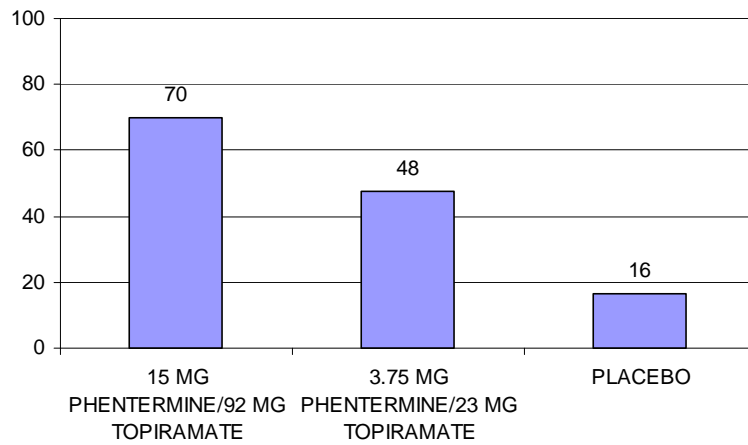
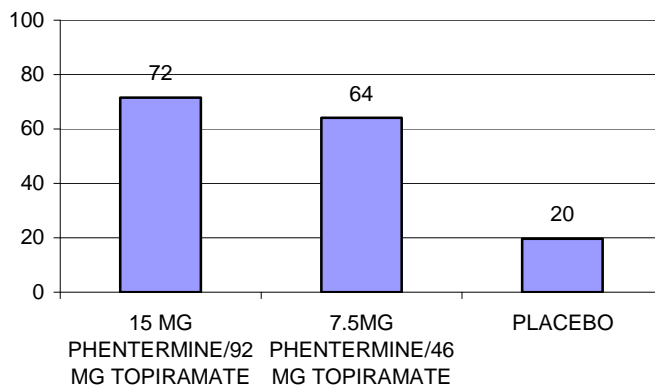


Figure 12 Percentage of patients with $\geq 5\%$ weight loss at Week 56 – MITT, LOCF Study 303



Other endpoints

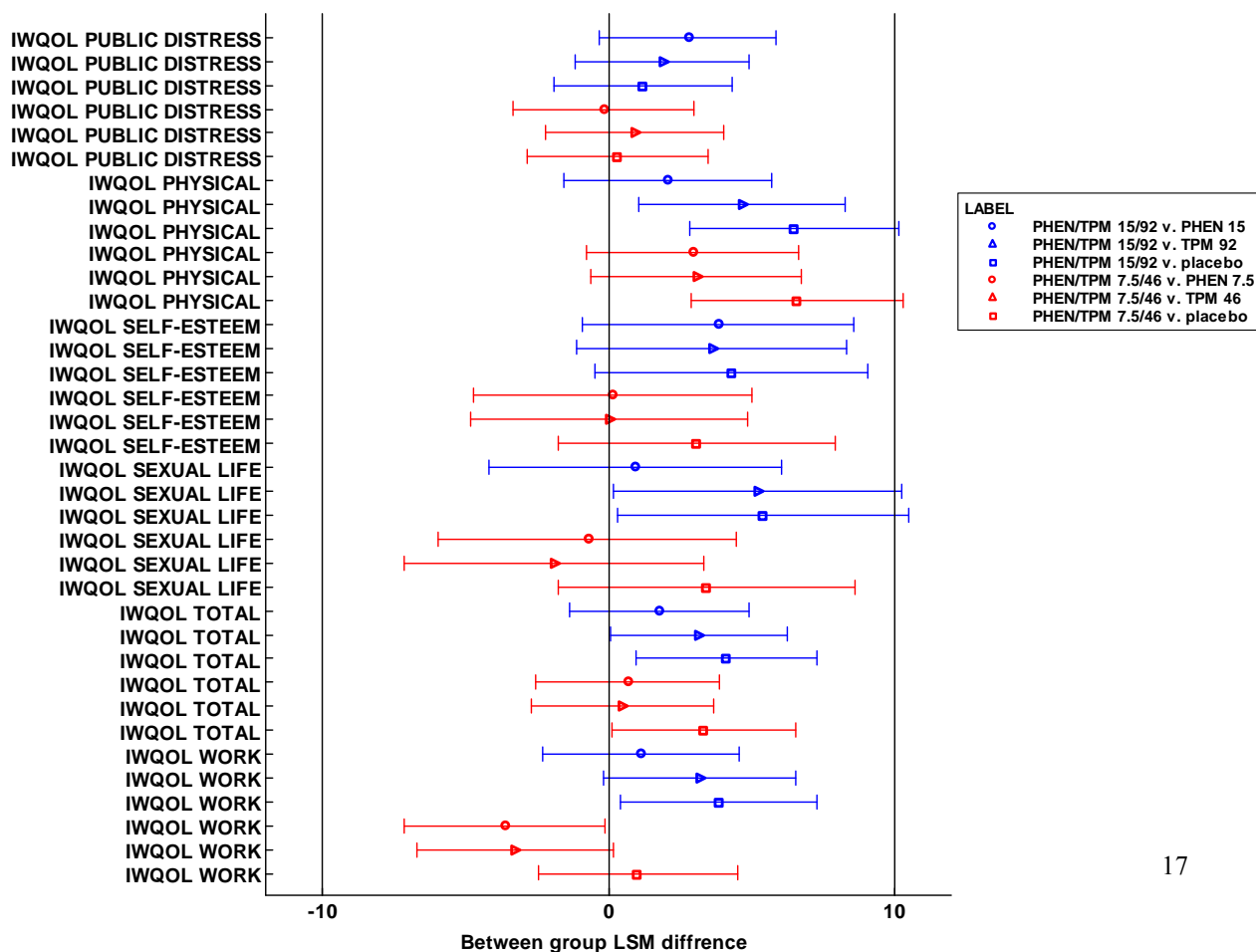
Figures 13-16 display treatment differences between the combinations and components or placebo in change from baseline to week 28 (MITT, LOCF) for Study 301. Other than absolute changes in weight and waist circumference, none of the endpoints was significantly different from both of the respective components and the placebo for both combination doses, PHEN/TPM 15/92 mg and 7.5/32 mg. Figure 17 displays the treatment differences between the combinations and placebo for Studies 302 and 303. The components were not studied in the 2 trials.

IWQOL-Lite

The IWQOL-Lite is a 31-item, self-administered instrument to evaluate physical function, self-esteem, sexual life, public distress, and work. The IWQOL scores were mapped to a 0 to 100 scale by subtracting the observed score from the maximum value for the component, dividing by the range for the component, and multiplying by 100.

None of the combinations was statistically significantly different from placebo and both of the components.

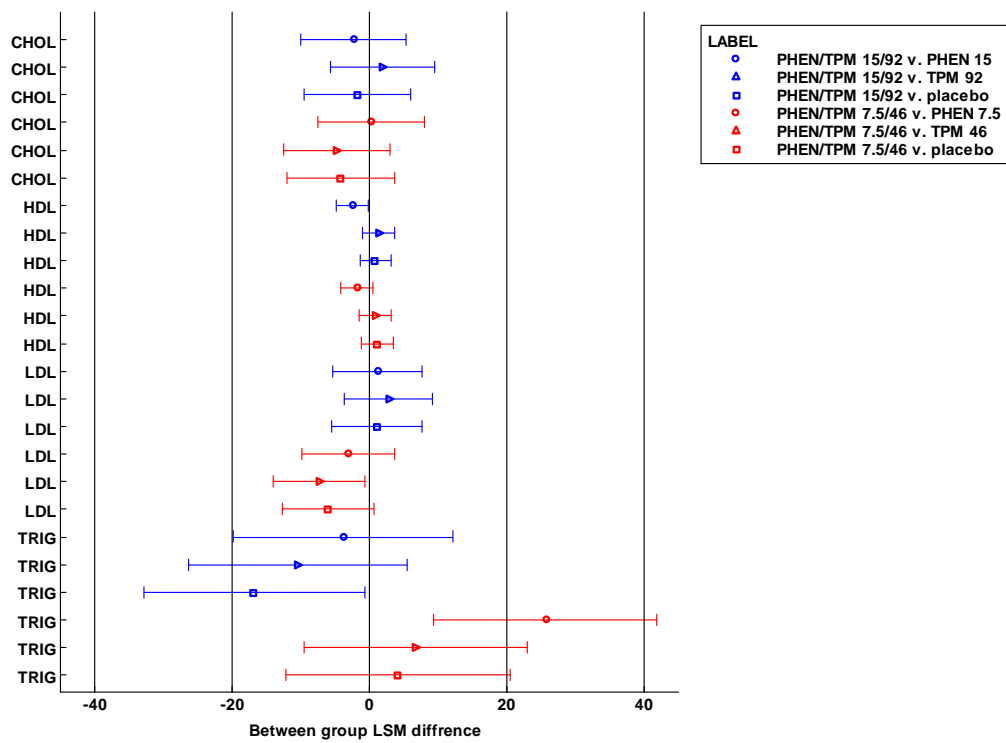
Figure 13 Between-group least squared mean difference (95% CI) – Study 301



Lipids

None of the combinations was statistically significantly different from placebo and both of the components. The triglycerides change from baseline was significantly worse in the PHEN/TPM 7.5/46 mg treatment group compared to the PHEN 7.5 mg treatment alone.

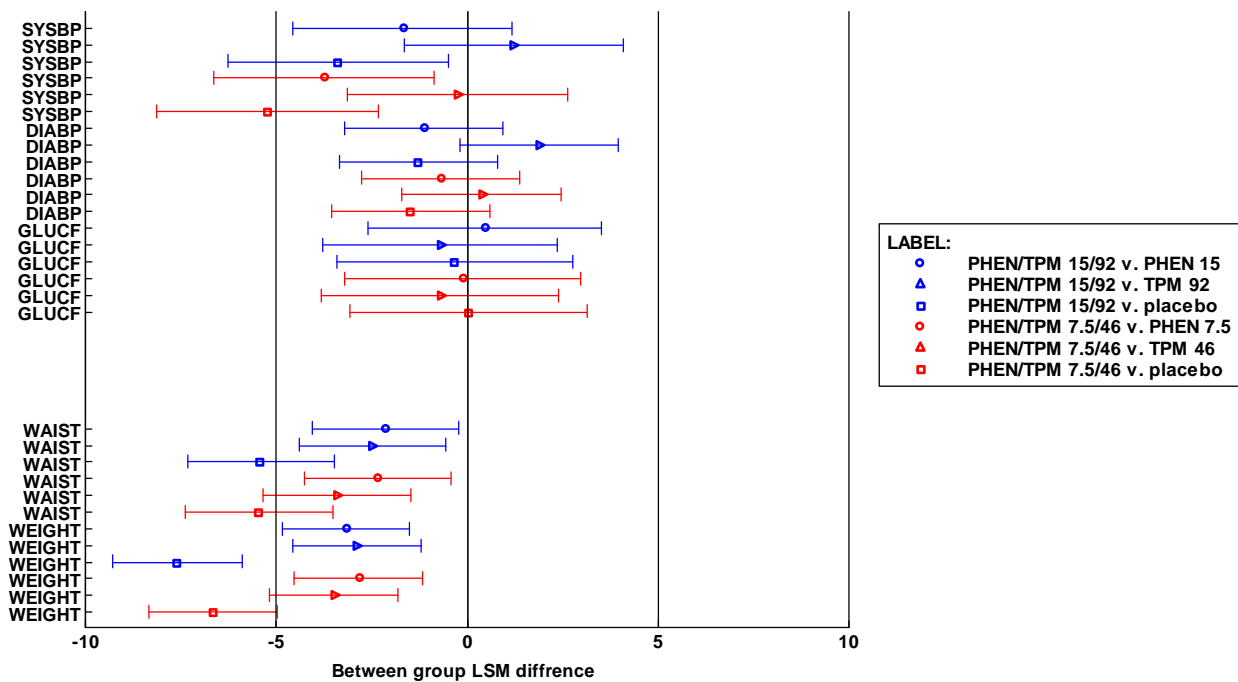
Figure 14 Between-group least squared mean difference (95% CI) – Study 301



SBP, DBP, FBG, Waist and Weight

Figure 15 shows only the absolute changes in weight and waist circumference were significantly different from their respective components and placebo for both combinations.

Figure 15 Between-group least squared mean difference (95% CI) – Study 301



HbA1c

The between group differences in HbA1c change from baseline was approximately -0.1% for the PHEN/TPM 7.5/46 mg compared to placebo and the components.

Figure 16 Between-group least squared mean difference (95% CI) – Study 301

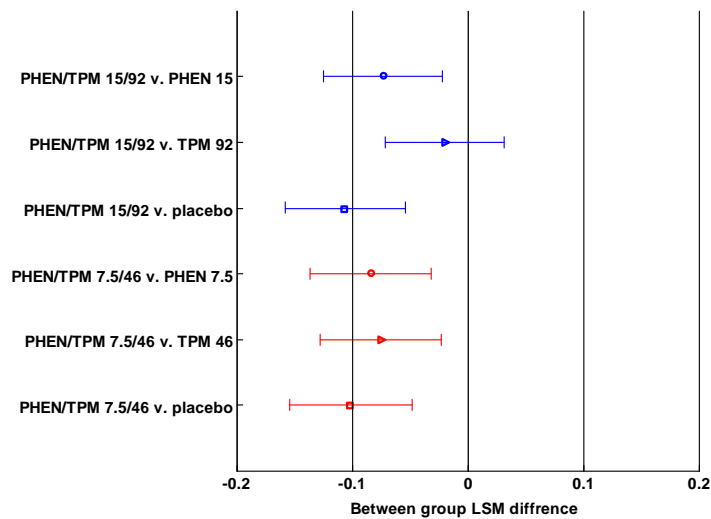
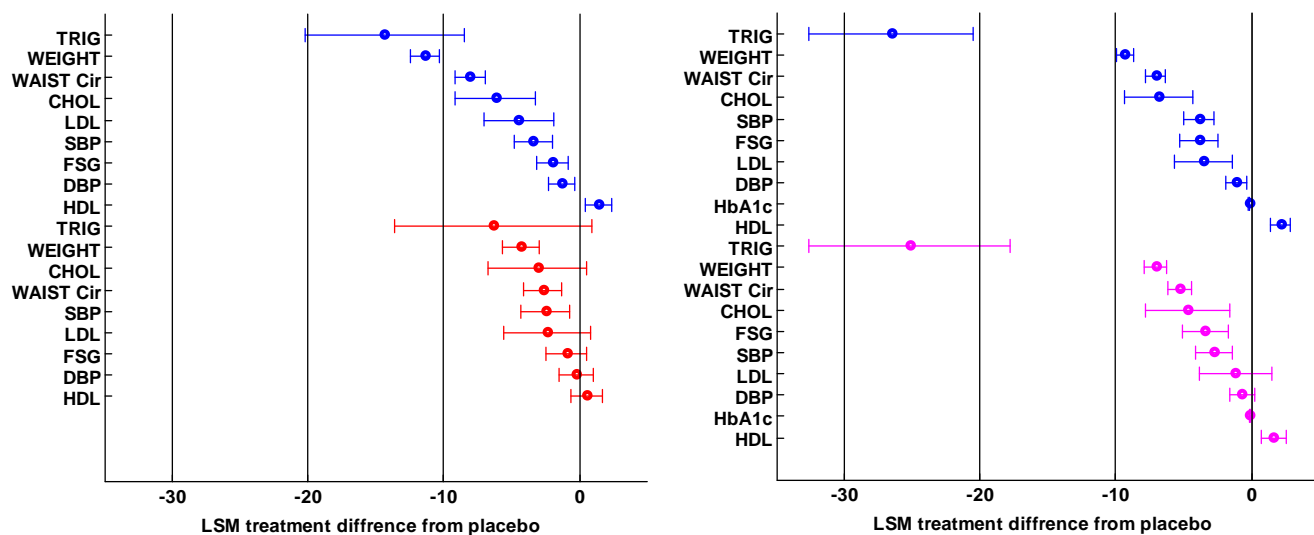


Figure 17 LSM difference (95% CI) from placebo

Study 302

Study 303

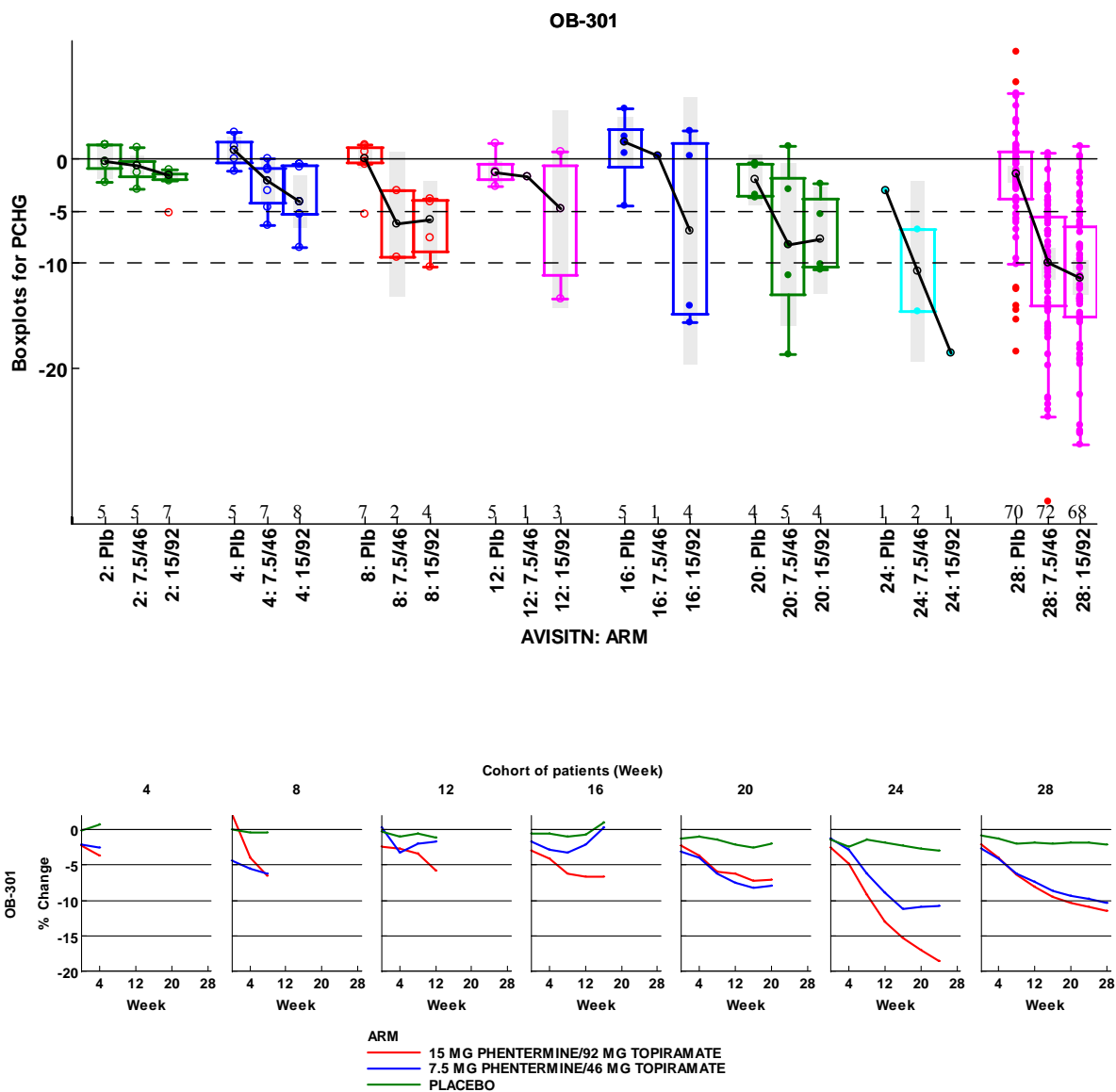


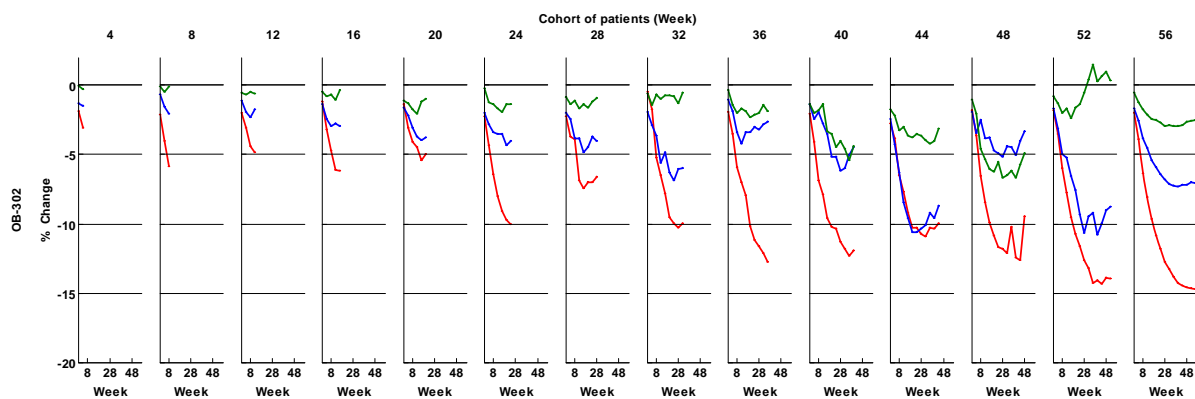
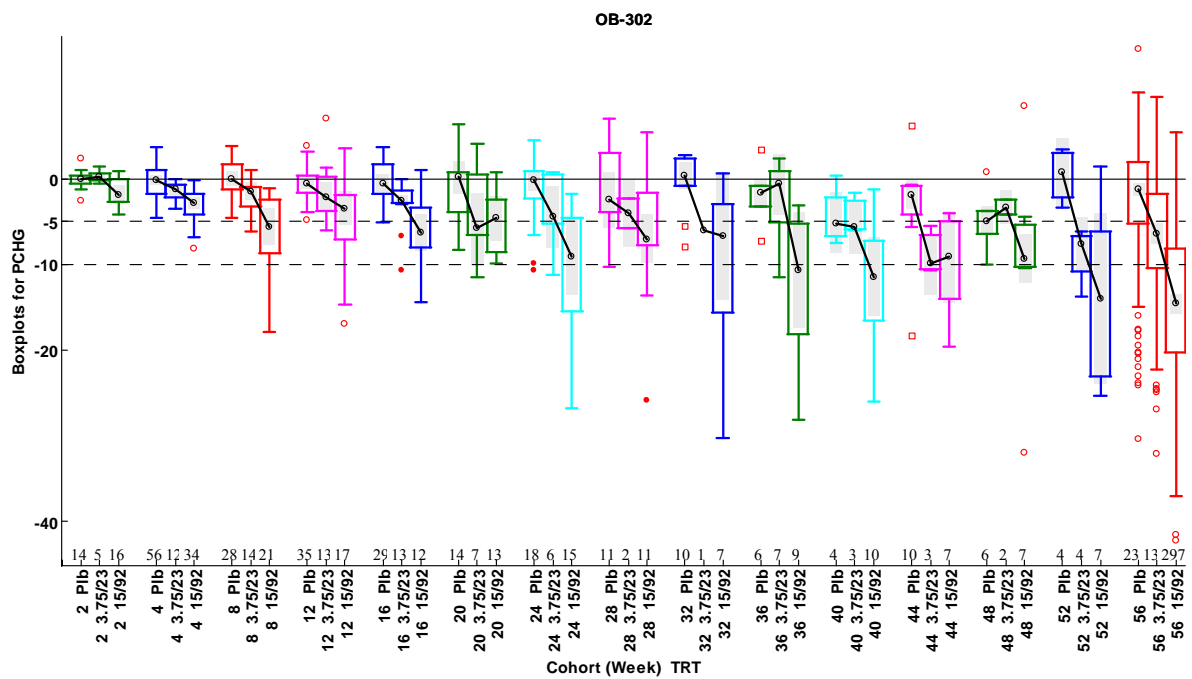
ARM:

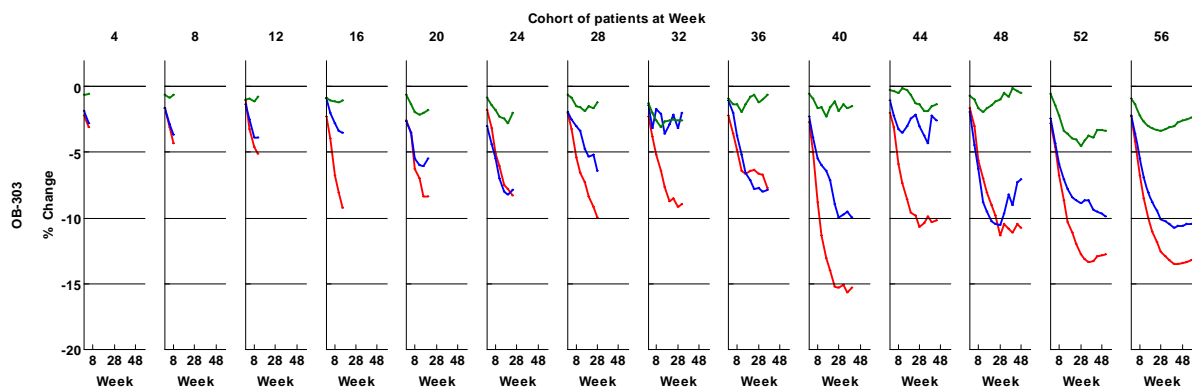
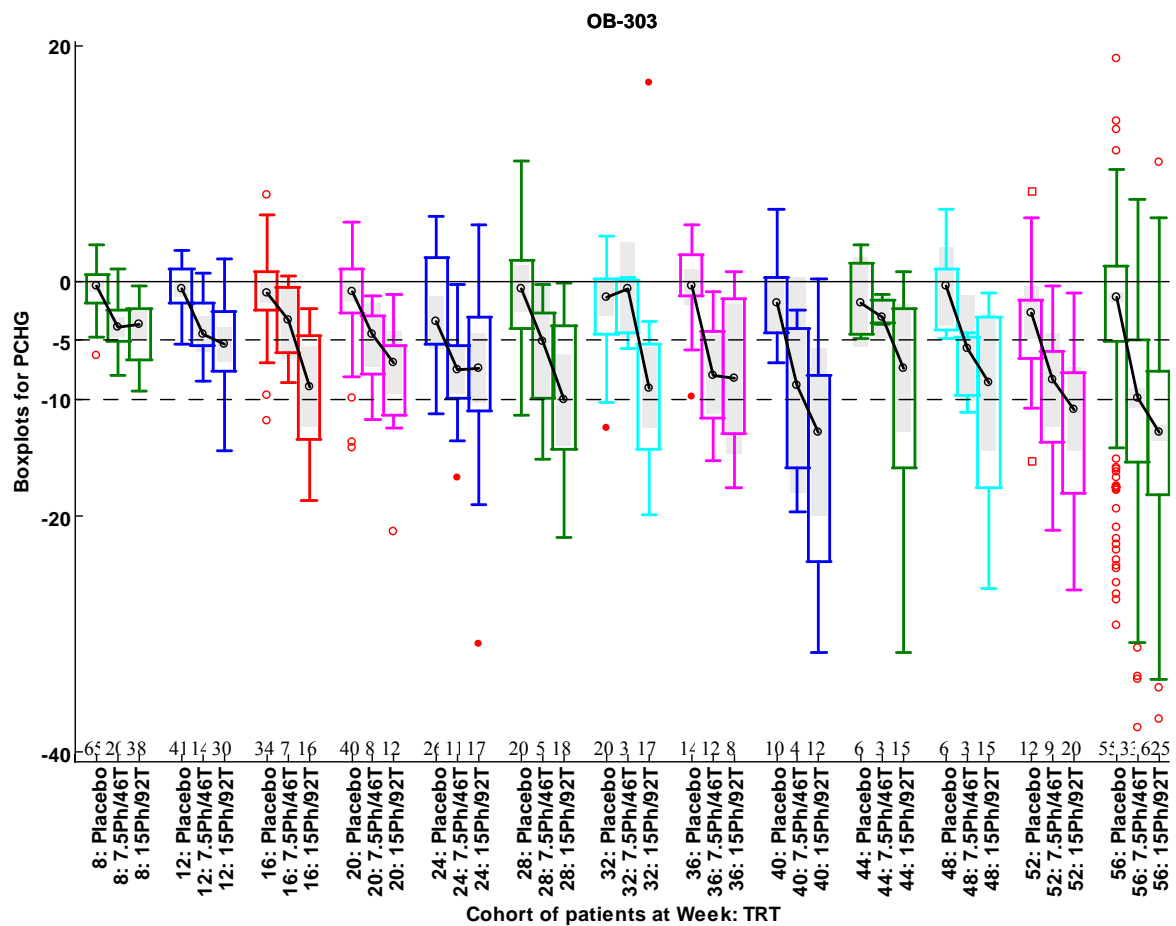
- 15 MG PHENTERMINE/92 MG TOPIRAMATE
- 3.75 MG PHENTERMINE/23 MG TOPIRAMATE
- 7.5 MG PHENTERMINE/46 MG TOPIRAMATE

Comparing cohort of patients

Approximately 40% of patients discontinued study medication. The following graphs show different cohorts of patients defined by their last week on study. The graphs showed that the cohorts who discontinued medication were similar to the completers (last cohort) in trend of percent weight change from baseline.









DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: June 2, 2010 **Date Consulted:** April 14, 2010

From: Jeanine Best, MSN, RN, PNP
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OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Qnexa (phentermine/topiramate) Controlled Release Capsules, NDA 22-580

Subject: MHT Review of Qnexa

Materials Reviewed:

- Reproductive Risk databases:
 - REPROTOX[®]
 - TERIS (the Teratogen Information Service)
- LactMed (the Drugs and Lactation Database)
- Draft Qnexa Labeling, submitted December 28, 2009
- Draft Proposed Qnexa REMS, submitted December 28, 2009, revised May 24, 2010

Consult Question: DMEP requests MHT input for Qnexa on the following:

- Labeling for pregnancy (including pregnancy category classification) and nursing mothers subsections
- Development of a pregnancy exposure registry
- Possible clinical lactation study
- Development of a pregnancy prevention plan

EXECUTIVE SUMMARY

This consult review provides the Pediatric and Maternal Health Staff - Maternal Health Team's (MHT) responses to consult questions from the Division of Metabolic and Endocrine Product's (DMEP) for Qnexa (phentermine/topiramate) Controlled Release Capsules regarding:

- Qnexa pregnancy category classification and pregnancy and nursing mothers labeling recommendations (specific labeling recommendations will be provided as an addendum to this review at a later date),
- Development of a pregnancy exposure registry
- Consideration of a lactation study
- Development of a pregnancy prevention plan.

Vivus, Inc. proposed a pregnancy category C classification in labeling for Qnexa because the two FDA-approved drug products that are in Qnexa, phentermine and topiramate, are currently classified as pregnancy category C drugs. However Vivus, Inc. also included pregnancy warnings and precautions in labeling for Qnexa that are typically associated with a pregnancy category D or X drug.¹ A Pregnancy Category C designation does not routinely trigger in Warnings and Precautions or Contraindications. A drug is classified as pregnancy category C when animal reproduction studies have shown an adverse embryofetal effect, there are no adequate and well controlled studies in pregnant women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. A drug may also be classified as pregnancy category C if animal studies have not been conducted and there are no adequate and well controlled studies in pregnant women. Phentermine is a DESI drug; no animal studies were conducted, and limited human data have shown no increase in congenital malformations. Phentermine was classified as a pregnancy category C drug because of lack of animal or human data. However, phentermine has pharmacologic activity similar to amphetamines, and concerns exist regarding the effects of amphetamine-induced vasoconstriction on mother, placenta, and fetus. Due to these concerns, phentermine labeling includes a recommendation against use in pregnancy, a recommendation that is inconsistent with pregnancy category C classification. Topiramate has demonstrated selective animal teratogenicity and embryotoxicity at clinically relevant doses, and limited human data have shown a possible increased risk in major malformations (cleft palate). Topiramate is also associated with metabolic acidosis and metabolic acidosis during pregnancy can cause fetal harm. Even with these potential risks, the clinical benefits to a pregnant woman for the approved indications of epilepsy or migraine prophylaxis may outweigh the potential fetal risks.

Weight loss drug products offer no clinical benefit if used in pregnancy, because a minimum weight gain is required during pregnancy due to the obligatory weight gain that occurs in maternal tissues (the uterus, breasts, blood volume, and in the fetal-placental unit). Also, concerns exist regarding the metabolic consequences of weight loss in pregnancy and potential effects on neurodevelopmental outcomes in childhood.

A drug product like Qnexa, which may increase the risk for adverse pregnancy outcomes and offers no clinical benefits for use during pregnancy, should be contraindicated for use during pregnancy and labeled as pregnancy category X. When such a drug is likely to be used in

¹ See Appendix A for FDA pregnancy Category Definitions

women of childbearing potential, the drug should have accompanying pregnancy prevention recommendations or strategies in place at the time of initial marketing. The selection of a particular pregnancy prevention strategy is generally based on a drug's indication(s), likely use in women of childbearing potential, and risk/benefit considerations of a drug if used during pregnancy. Information is needed both on effective contraception methods and types of contraception methods that are acceptable to and appropriate for women who will use Qnexa for the treatment of obesity. This information will be crucial for the success of pregnancy prevention with Qnexa use.

Thirty-four pregnancies occurred in the Qnexa clinical development program, despite a requirement for the use of two forms of contraception; therefore, it is likely that pregnancies will occur with Qnexa treatment, even with appropriate pregnancy prevention recommendations and risk mitigation strategies. Information should be collected on Qnexa exposure during pregnancy in order to provide clinically relevant human data to inform labeling. A drug-based pregnancy exposure registry (a prospective observational cohort study) would be the appropriate mechanism to use to collect Qnexa pregnancy exposure data.

Qnexa is systemically available and will be used women of childbearing potential, including lactating women. Adequate information is not available regarding the drug's concentration in milk and the estimated infant daily dose of drug available through human milk. Limited human lactation data is available for topiramate show that infant plasma topiramate levels are 10-20% of the maternal plasma level. No human lactation data are available for phentermine; however, because phentermine has pharmacologic properties similar to amphetamines, current labeling recommends against human milk feeding. A milk-only clinical lactation trial would provide information on the concentration of Qnexa (phentermine and topiramate) in human milk and the estimated infant daily dose of the drug through human milk to inform labeling for lactation risk/benefit decision making.

In summary, the MHT has the following recommendations for Qnexa:

1. Classify Qnexa as Pregnancy Category X - There are potential fetal risks and no acceptable clinical benefits for a woman using Qnexa in pregnancy.
2. Require that the Qnexa Risk Evaluation Mitigation and Strategy (REMS) have a goal for pregnancy prevention. Pregnancy prevention and related recommendations should be placed in labeling, including the Medication Guide for patients. The Sponsor should provide recommendations for effective contraception use during Qnexa therapy.
3. Require a pregnancy registry (a prospective observational cohort study) as a Postmarketing Requirement (PMR).
4. Require a milk-only lactation trial as a Postmarketing Requirement (PMR).
5. The MHT will provide pregnancy, nursing mothers, and information for females of childbearing potential labeling recommendations for Qnexa as an addendum to this

review at a later date. Labeling will be done in collaboration with the DMEP Qnexa Pharmacology/Toxicology Reviewers.

INTRODUCTION

Vivus, Inc. submitted NDA 22-580, a 505(b)(2) application, on December 28, 2009, for Qnexa (phentermine/topiramate) Controlled Release Capsules for the following indication:

“the treatment of 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 ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight patients ($\text{BMI} \geq 27 \text{ kg/m}^2$) with weight-related co-morbidities such as hypertension, type 2 diabetes, dyslipidemia, or central adiposity (abdominal obesity)”.²

Qnexa (phentermine/topiramate) Controlled Release Capsules is a fixed-dose combination of immediate-release phentermine hydrochloride beads and modified-release topiramate beads proposed in the doses of 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg, respectively, for dose titration.

Vivus, Inc. submitted a required Risk Evaluation and Mitigation Strategy (REMS)³ for Qnexa because a REMS is required for all antiepileptic drugs (AEDs) to inform patients, physicians and pharmacists of the potential risk for suicidal thoughts and behavior with AED treatment. Topiramate, a component of Qnexa is an AED. A revised draft Qnexa REMS was submitted May 24, 2010, with additional proposed goals, including appropriate patient selection; education of patients and healthcare providers regarding safe use and potential side effects and the use of Qnexa with a comprehensive weight management program; and, education of healthcare providers regarding dosing and titration requirements. Proposed REMS elements include a Medication Guide, a Communication Plan, REMS Assessments, and Postmarketing Surveillance.

Phentermine and topiramate are both FDA-approved drug products and both are classified as Pregnancy Category C drugs based on animal data and the risk/benefit considerations for the indicated populations if used during pregnancy (topiramate, approved for epilepsy and migraine prophylaxis), and no animal or human data (phentermine, approved for weight loss). Vivus, Inc. was requested to classify Qnexa as a Pregnancy X drug because the positive animal findings with topiramate and the risk/benefit consideration for use in pregnancy for the indication of treatment of obesity.⁴

The Division of Metabolic and Endocrine Products (DMEP) consulted the Maternal Health Team (MHT) of the Pediatric and Maternal Health Staff on April 6, 2010 to provide input on:

- Qnexa pregnancy and nursing mothers labeling, including the pregnancy category classification,
- Development of a pregnancy exposure registry
- Consideration of a lactation study

² See draft Qnexa labeling submitted December 28, 2009

³ See draft Qnexa REMS, December 28, 2009

⁴ See P-IND Meeting Minutes, IND 69,718, November 1, 2004

- Development of a pregnancy prevention plan.

Thirty-four women became pregnant while participating in Qnexa clinical trials despite a study requirement for females of childbearing potential to use two forms of contraception while on study drug. Qnexa will be discussed at a July 15, 2010, Advisory Committee Meeting.

BACKGROUND

Phentermine

Phentermine, NDA 11-613, a sympathomimetic amine used as an anorectic or appetite suppressant in obesity treatment, with pharmacologic activity similar to amphetamines, was initially approved on May 4, 1959, under the tradename Ionamin[®] (UCB, Inc.) and was found to be effective under DESI on July 19, 1974. Ionamin[®] was withdrawn from the market (for reasons other than safety and efficacy) in 2008. Phentermine is the most commonly prescribed medication for treatment of obesity in the U.S.⁵ and is currently marketed under several ANDAs. The referenced phentermine product for this combination 505(b)(2) application is Adipex-P[®], ANDAs 88-023 (37.5 mg oral capsule) and 88-128 (37.5 mg oral tablet). Adipex-P[®] is indicated:⁶

*as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia).*⁷

Phentermine is also marketed in 30 and 50 mg dose tablets and/or capsules by other generic manufacturers.

Adipex-P[®] is currently classified as a pregnancy category C drug. No animal reproductive studies or studies in pregnant women have ever been conducted with phentermine. Limited human pregnancy data was located in reproductive risk databases. REPROTOX[®]⁸ summarizes phentermine reproductive risk as follows:

There are small series of human pregnancies exposed to phentermine without an increase in congenital malformations. Phentermine is avoided during pregnancy due to concerns about effects of weight loss on embryo development.

The Teratogen Information Service (TERIS)⁹ summarizes phentermine reproductive risk as follows:

⁵ Hendricks EJ, Rothman RB, Greenwaw FL. How physician obesity specialists use drugs to treat obesity. Obesity 2009 Sep;17(9):1730-5

⁶ See Adipex-P Labeling, last revised 7/2005

⁷ See Adipex-P Labeling, last revised 7/2005

⁸ REPROTOX[®] is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPROTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development.

⁹ TERIS is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women.

The magnitude of teratogenic risk to child born after exposure during gestation is undetermined and the quality and quantity of data on which the risk estimate is based is limited. Comments: 1) Dieting during early pregnancy (without taking vitamins) may increase the risk of folate-sensitive malformations in the fetus; 2) The risk of congenital anomalies may be increased in the children of obese women.

Phentermine has pharmacologic activity similar to amphetamines so it is important to consider amphetamine vascular side effects, including vasoconstriction and a rise in blood pressure, on a pregnancy. REPROTOX[®]¹⁰ reports that studies in pregnant sheep with methamphetamine demonstrated the following:

Drug administration in this model is associated with an elevation in maternal and fetal blood pressure, and a decrease in fetal oxyhemoglobin saturation and pH. A transient increase in umbilical vascular resistance and a decrease in uterine blood flow accompanied these changes.

Current approved Adipex-P[®] Pregnancy and Nursing Mothers Labeling:

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproduction studies have not been conducted with ADIPEX-P[®]. It is also not known whether ADIPEX-P[®] can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. ADIPEX-P[®] should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer Comment:

No information on the excretion of phentermine into human milk or on the estimated infant daily dose was listed in The Drugs and Lactation Database (LactMed).¹¹ The American Academy of Pediatrics (AAP) Committee on Drugs recommends against human milk-feeding with amphetamines when they are used as drugs of abuse should not be used by nursing mothers because of the adverse effects to the infant. The AAP considers stimulants as drugs that should be used in nursing mothers with caution because of potential infant adverse effects and the unknown effect on infant neurologic development.¹²

¹⁰ REPROTOX[®] is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPROTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development. Available through MicroMedex

¹¹ See toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

¹² American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. 2001 Sep; 108(3):776-89

Topiramate

Topiramate, a monosaccharide sulfamate and an antiepileptic drug (AED), was approved on December 24, 1996, under the tradename Topamax[®] (Ortho-McNeil-Janssen Pharmaceuticals, Inc.). The referenced topiramate NDAs for the combination 505(b)(2) applications are NDA 20-505 (25 mg, 50 mg, 100 mg, and 200 mg tablets) and NDA 20-844 (15 mg and 25 mg oral capsules). TOPAMAX[®] is indicated for the following conditions:¹³

- *Monotherapy epilepsy: Initial monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic-clonic seizures).*
- *Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients ≥ 2 years of age with seizures associated with Lennox-Gastaut syndrome (LGS).*
- *Migraine: Treatment for adults for prophylaxis of migraine headache)¹⁴*

The recommended TOPAMAX[®] adult doses are (all doses should be titrated up to the recommended daily dose):

- 400 mg/day give in two divided doses for monotherapy in epilepsy and for adjunctive therapy in primary generalized tonic-clinic seizures
- 200 to 400 mg/day in two divided doses for adjunctive therapy in epilepsy with partial onset seizures
- 100 mg/day in two divided doses for migraine prophylaxis¹⁵

Topiramate is currently used off-label for weight loss purposes.¹⁶ The exact mechanism of action through which topiramate effects weight loss remains unclear. Hypothesized mechanisms of action include: increased energy expenditure secondary to anorexia; reduction in the activity of salivary enzymes, which are partially responsible for taste; reduction in leptin and corticosteroid concentrations; and reduction in blood glucose and insulin concentrations.¹⁷

Topamax[®] (topiramate) is classified as a pregnancy category C drug based on animal developmental reproductive and toxicology studies and the risk/benefit of use during pregnancy for the approved indications (benefit may outweigh the risk in pregnant patients with epilepsy or migraine). The pregnancy subsection of Topamax[®] labeling was revised on December 22, 2009, to include information on the effect of metabolic acidosis in pregnancy and the possible association with fetal harm, as topiramate use is associated with metabolic acidosis. In addition the nursing mothers subsection was updated to include limited human lactation data.

Woman who take topiramate during pregnancy are encouraged to enroll in the North American Antiepileptic Drug (AED) Pregnancy Registry, a registry that is designed to obtain and publish

¹³ See current approved Topamax labeling, December 22, 2009

¹⁴ See current approved Topamax labeling, December 22, 2009

¹⁵ See current approved Topamax labeling, December 22, 2009

¹⁶ Ioannides-Demos L, Proietto J, McNeill J. Pharmacotherapy for obesity. *Drugs* 2005; 65 (10): 1391-1418

¹⁷ Goldfarb B. Topiramate and weight loss...Does it work? *DOC News, Diabetes Journals*, Jan 2005; 2(1)

information on the frequency of major malformations among infants whose mothers have taken one or more AEDs for any medical condition.

Limited human pregnancy data was located in reproductive risk databases. REPROTOX[®] ¹⁸ summarizes topiramate reproductive risk as follows:

Topiramate produces abnormal pregnancy outcome in experimental animals. Human case reports and case series have identified both normal and abnormal pregnancy outcome after topiramate exposure, without a clear increase in the incidence of congenital anomalies.

TERIS¹⁹ summarizes topiramate reproductive risk as follows:

The magnitude of teratogenic risk to a child born after exposure during gestation is minimal to small and the quality and quantity of data on which the risk estimate is based is limited to fair.

In addition, the following information comes from preliminary experience from the UK Epilepsy and Pregnancy Register.²⁰

The number of outcomes of human pregnancies exposed to topiramate is low, but the major congenital malformation rate for topiramate polytherapy raises some concerns. Overall, the rate of oral clefts observed was 11 times the background rate. Although the present data provide new information, they should be interpreted with caution due to the sample size and wide confidence intervals.

Current approved Topamax[®] Pregnancy, Labor and Delivery, and Nursing Mothers Labeling:²¹

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Topiramate may cause serious adverse fetal effects, based on clinical and nonclinical data. Topiramate treatment is associated with metabolic acidosis [see Warnings and Precautions (5.4)]. The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) may be associated with decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the nonpregnant state [see Warnings and Precautions (5.4)]. Newborns of mothers treated with topiramate should be

¹⁸ See REPROTOX[®]. Available through MicroMedex

¹⁹ TERIS is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women.

²⁰ Hunt S, Russell A, Smithson W, Parsons L, et al. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2008 July 22;71(4):272-276

²¹ See current approved Topamax labeling, December 22, 2009

monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

There are no studies using TOPAMAX[®] in pregnant women. TOPAMAX[®] should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in multiple animal species at clinically relevant doses. When oral doses of 20, 100 or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD) 400 mg/day on a mg/m² basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m² basis) or greater during the organogenesis period of pregnancy. Embryo toxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m² basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m² basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m² basis) and reductions in pre-and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m² basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30 or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m² basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m² basis) and higher.

Pregnancy Registry

The North American Drug Pregnancy Registry has been established to collect information and provide scientific knowledge about safety and outcomes associated with

pregnant women being treated with antiepileptic drugs. It is desirable that the experience from patients who are exposed to topiramate during pregnancy be reported to this registry. Such information can be reported to the North American Drug Pregnancy Registry by either a healthcare provider or the patient by calling 1-888-233-2334. Information about the North American Drug Pregnancy Registry can be found at <http://www.massgeneral.org/aed/>.

8.2 Labor and Delivery

Although the effect of TOPAMAX[®] on labor and delivery in humans has not been established, the development of topiramate-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus' ability to tolerate labor [see Pregnancy (8.1)].

8.3 Nursing Mothers

Limited data on 5 breastfeeding infants exposed to topiramate showed infant plasma topiramate levels equal to 10-20% of the maternal plasma level. The effects of this exposure on infants are unknown. Caution should be exercised when administered to a nursing woman.

Lastly, Topamax labeling includes the following drug interaction information with oral contraceptives:

7 DRUG INTERACTIONS

7.3 Oral Contraceptives

Exposure to ethinyl estradiol was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when TOPAMAX was given as adjunctive therapy in patients taking valproic acid). However, norethindrone exposure was not significantly affected. In another pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX, given in the absence of other medications at doses of 50 to 200 mg/day, was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding [see Clinical Pharmacology (12.5)].

Pregnancy Exposure Registries

A pregnancy exposure registry²² is a prospective observational cohort study that actively collects information on a medical product exposure during pregnancy and associated pregnancy outcomes. This is one method of collecting data on drug exposure during pregnancy before pregnancy outcomes are known. The main goal of pregnancy exposure registries is to collect data about the presence or absence of drug-associated adverse developmental effects when a

²² See Guidance for Industry – Establishing Pregnancy Exposure Registries, August 2002

drug is used during pregnancy. This data is used in labeling to inform clinician and patient decision making regarding use of the product. Drug products that are considered good candidates for pregnancy exposure registries include those that have a high likelihood of use by women of childbearing potential. Pregnancy exposure registries are unlikely to be warranted when the product is not used or rarely used by women of childbearing potential.

The decision to establish a pregnancy exposure registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the registry. In order to collect meaningful data, the sample size of a pregnancy exposure registry should be large enough to either detect a difference or show no difference between the exposed and control groups.²³ Pregnancy exposure registries can be drug-based or a disease-based.

The North American Antiepileptic Drug (AED) Pregnancy Registry²⁴ was established in 1997 for pregnant women in the U.S. and Canada at Massachusetts General Hospital to determine the safety of seizure medications when taken by women during pregnancy and to obtain and publish information on the frequency of major malformations among infants whose mothers took one or more AEDs during pregnancy for any medical condition. Information on the American Antiepileptic Drug Pregnancy Registry is included in the labeling for topiramate and other AED products, and AED Pregnancy Registry information receives preferential placement in labeling over other pregnancy drug exposure registries.

Clinical Lactation Trials

Clinical lactation trials can provide much needed data on which to base human milk feeding and drug treatment decisions. These data include the concentration of drug in human milk and the estimated infant daily dose of drug through human milk. Ideally, clinical lactation data should be available to inform labeling for all drugs likely to be used by lactating women or by women of child-bearing age. Currently, lactating women and their health care providers often make decisions about whether to continue human milk feeding during drug treatment in the absence of data. To take needed drug therapy, a mother may stop human milk feeding unnecessarily, thereby sacrificing the known benefits for her and her infant. In 2005, FDA published a draft Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling. This Guidance has been revised for publication as a Final Guidance that is currently in clearance. The Guidance refers to “clinical lactation trials” (rather than studies) and includes a simplified approach to conducting lactation studies based on existing information about human milk-feeding and the transfer of drugs into human milk.

The Guidance recommends the conduct of a clinical lactation trial in the following circumstances:

- Original or supplemental review of a drug where use is expected by women of childbearing potential. This may include drugs used to treat relatively rare conditions that occur predominantly in women of childbearing age and require chronic drug therapy for disease control, such as multiple sclerosis.

²³ See Guidance for Industry: Establishing Pregnancy Exposure Registries, August 2002

²⁴ Holmes L, Wyszynski D. North American Antiepileptic Drug Pregnancy Registry. *Epilepsia*, 2004; 45 (11):1465

- Use of a drug by lactating women becomes evident following marketing approval (e.g., via reports in the medical literature or lay press)
- Use of marketed drugs commonly used by women of childbearing potential, including but not limited to antidepressants, antipsychotics, antihypertensives, anti-infectives, asthma drugs, and diabetic and pain drugs.²⁵

Clinical lactation trials are usually conducted in the postmarketing setting of maternal therapeutic drug use.

Pregnancy and Weight Gain Guidelines

Weight gain guidelines exist for pregnancy because both excessive weight gain and weight loss or poor weight gain during pregnancy have been associated with adverse maternal and fetal outcomes. The Institute of Medicine (IOM) published the following new pregnancy weight gain guidelines in May 2009, to address current research that had been conducted on the effects of weight gain in pregnancy on the health of both mother and baby.²⁶

TABLE S-1 New Recommendations for Total and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI

Pregpregnancy BMI	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
	Range in kg	Range in lbs	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (< 18.5 kg/m ²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m ²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m ²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥ 30.0 kg/m ²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

An obligatory weight gain occurs in maternal tissues (the uterus, breasts, blood volume, and in the fetal-placental unit) during pregnancy. Weight gain in pregnancy is partly a gain in adipose tissue, accompanied by some degree of insulin resistance and other metabolic alterations that serve as an adaptive response to allow a more efficient transfer of fuels across the placenta to the fetus.

Excessive weight gain during pregnancy can lead to an increased risk of maternal insulin resistance and gestational diabetes mellitus which can lead to fetal hyperglycemia and increased adiposity. In addition, these babies have a higher risk for childhood obesity and accompanying metabolic sequelae.²⁷ Pre-pregnancy obesity is associated with an increased risk of major malformations, including neural tube defects, omphalocele, heart defects, orafacial clefts, and others. The mechanism for these observed malformations and obesity is not known but may be

²⁵ See draft Guidance for Industry: Clinical Lactation Studies – Study Design, data Analysis, and recommendations for Labeling, February 2005

²⁶ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: <http://nap.edu/catalog/12584.htm>

²⁷ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: <http://nap.edu/catalog/12584.htm>

due to severe metabolic and hormonal alterations including hyperglycemia, elevated insulin, and elevated estrogen levels; nutritional deficits from dieting or poor quality diets; and/or diabetes.²⁸

Despite the association between obesity and major fetal malformations, a minimum weight gain (and no weight loss) is recommended during pregnancy for all women, including those who are already overweight or obese because of the obligatory weight gain that occurs in maternal tissues during pregnancy. The metabolic consequences of weight loss in pregnancy may be associated with adverse neurodevelopmental outcomes in childhood.²⁹

Pregnancy Planning and Prevention

Fifty percent of pregnancies in the U.S. are unplanned and may result in inadvertent fetal drug exposure.³⁰ Approximately, half of these unintended pregnancies occur in women who use some type of contraceptive, usually due to suboptimal contraceptive compliance.³¹

FDA has required varying pregnancy planning and prevention risk mitigation strategies for drugs that are known or highly suspected human teratogens. In an attempt to prevent fetal drug exposure, these risk mitigation strategies range from routine measures, such as labeling, to stringent measures with requirements in place for prescribing and dispensing the product. The design of a particular risk mitigation strategy is generally based on a drug's indication(s), its likelihood of use in women of childbearing potential, and the risk/benefit considerations of the drug if used during pregnancy. The iPLEDGE program for isotretinoin³² (a known human teratogen with use mainly in a female of childbearing potential population) is an example of a stringent pregnancy prevention program. Despite rigorous program requirements for females of childbearing potential, including educational requirements, pregnancy testing, and specific contraception use, pregnancies continue to occur in the iPLEDGE program³³ and the pregnancy rate increased from the first to the second year of the program (the third year pregnancy rate was similar to the second year rate).^{34,35} Tsur and Berkovitch³⁶ and Boucher and Beaulac-Baillargeon³⁷ looked at contraceptive compliance in women of childbearing age using isotretinoin and found that, while most women understood the pregnancy prevention recommendations when provided, most women did not comply with the recommendations, and very few women used the required two forms of contraception simultaneously. Both authors concluded that more information is needed to understand women's noncompliance with

²⁸ Watkins M, Rasmussen S, et al. Maternal obesity and the risk for birth defects. *Pediatrics* 2003; 111:1152-58

²⁹ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: <http://nap.edu/catalog/12584.htm>

³⁰ Alan Guttmacher Institute. Unintended pregnancy in the United States. *Family Planning Perspectives*. 1998 Jan-Feb;30(1):24-9, 46

³¹ Dardano K, Burkman R. Contraceptive Compliance, *Obstetrics and Gynecology Clinics of NA*, 2000 Dec;27(4):933-41

³² See current approved Accutane labeling, February

³³ iPLEDGE Program information is not publically disclosable at this time

³⁴ See MHT 2 Year iPLEDGE Review, February 19, 2009

³⁵ See OSE Year 3 iPLEDGE Assessment, January 12, 2010

³⁶ Tsur K, Berkovitch M. The effect of drug consultation center guidance on contraceptive use among women using isotretinoin: a randomized controlled study. *Women's Health*, 2008 May;17(4):579-84.

³⁷ Boucher N, Beaulac-Baillargeon L. Pregnancy prevention among women taking isotretinoin: failure to comply with the recommendations. *Can Fam Physician*, 2006 Mar;52:338-9.

contraception and strategies are needed to increase contraceptive adherence among women of childbearing age.

Obesity presents its own contraceptive challenges. Conflicting data exist on the effects of obesity on the efficacy of contraception, especially on the efficacy of hormone contraceptives. Disease co-morbidities, including a higher risk for venous thromboembolism in obese women, may preclude the use of estrogen-containing hormonal contraceptives in some of these women.³⁸ Schraudenbach and McFall³⁹ performed a secondary analysis of data from the seven states participating in the Family Planning Module of the 2006 Behavioral Risk Factor Surveillance System (BRFSS). The study assessed whether body mass index (BMI) category is related to contraception use and type of contraception used in women of childbearing age. They found that use of hormonal contraception was highest among women with a BMI of 15 to 25, and use decreased with increasing age. Barrier methods of contraception were less likely to be used in all BMI categories, and use decreased with increasing age. Use of procedural contraception methods was higher among women with a BMI greater than 25, and use increased with increasing age. The authors concluded that further studies are needed to examine the relationship between the use of different types of contraception and body weight to better understand the benefits and obstacles of different contraception types. This knowledge could potentially inform development of more effective health promotion programs to decrease unintended pregnancies and improve pregnancy health outcomes.

A major challenge for all pregnancy prevention programs is to increase contraceptive compliance either through patient behavioral change or by increasing the use of contraceptive methods with efficacy that is more independent of daily user behavior (like IUDs and procedural contraceptive methods). To effect (influence and reinforce) behavior change and self-efficacy for pregnancy prevention, one must understand how the target audience links health and behavior, understand audience knowledge deficits, and use a behavioral theoretical framework(s) to design the actual program.⁴⁰

Pregnancy and Nursing Mothers Labeling

FDA currently classifies the reproductive and developmental risk of drugs for use during pregnancy into five categories (A, B, C, D, and X)⁴¹ using animal and human data (if available). Some of the categories consider the potential risk of the drug versus the potential benefit to a woman if used during pregnancy. Because of consideration of the potential risk/benefit of a specific drug for use during pregnancy, the classification system does not represent a linear increase in risk for pregnancy category A to pregnancy category X (see Appendix A for a description of each pregnancy category). The MHT notes that the pregnancy category classification will be eliminated when the Final Pregnancy and Lactation Labeling Rule (PLLR) publishes (Proposed Pregnancy and Lactation Labeling Rule published May 29, 2008).⁴² When the final regulations publish, the PLLR will complete the requirements on content and format of

³⁸ Murthy AS. Obesity and contraception: emerging issues. *Semin Reprod Med.* 2010 Mar;28(2):156-63

³⁹ Schraudenbach a, McFall A. Contraceptive use and contraception type in women by body mass index category. *Women's Health Issues* 2009 (19):381-89; www.whjournal.com

⁴⁰ Edberg M. *Essentials of Health Behavior: Social and Behavioral Theory in Public Health.* Jones and Bartlett Publishers Inc. 2007.

⁴¹ See Appendix A for pregnancy category definitions table

⁴² See Proposed Pregnancy and Lactation Labeling Rule, 73 FR 30831, May 29, 2008

labeling for human prescription drug and biological products (Physician Labeling Rule, January 24, 2006, 71 FR 3922) by revising the content and format requirements for the pregnancy, labor and delivery, and nursing mothers subsections of labeling. The proposed changes to prescription drug labeling will provide prescribers with clinically relevant and more comprehensive information for making prescribing decisions and for counseling women who are pregnant, human milk-feeding, or of childbearing age about using prescription medications.

Until the PLLR publishes, the Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations, including the assignment of pregnancy categories, but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

REVIEW OF DATA

Pregnancies in the Qnexa Clinical Development Program

Thirty-four pregnancies occurred in clinical trials with Qnexa despite a study requirement for females of childbearing potential to use a double-barrier method of contraception, a stable hormonal contraception plus a single barrier method, or have a tubal ligation, while on study drug. Fourteen of the pregnant women reported using an oral contraceptive along with a single barrier method of contraception (usually a condom); 18 of the women reported using a double barrier method of contraception (usually condoms and spermicidal gel); 1 woman reported that she switched from using an oral contraceptive with a single barrier method of contraception to a double barrier method of contraception; and contraception information on one woman is unknown. Urine pregnancy tests were obtained at screening, randomization, and dose titration and then every 4 weeks at regular treatment clinic visits.⁴³

Eighteen women delivered normal healthy infants; 3 women had spontaneous abortions; 10 women had elective terminations; 1 woman had an ectopic pregnancy; and 1 pregnancy was ongoing at the time of NDA submission; however, the fetus has been diagnosed with Down’s syndrome via pre-natal testing, including amniocentesis.

Reviewer Comment:

Down syndrome is a chromosomal disorder caused by an error in cell division that results in the presence of an additional third chromosome 21. The National Institute of Child Health and Development (www.nichd.nih.gov) reports that Down’s Syndrome is a random event and occurs in one out of 800 live births in all races and economic groups, and incidence increases with

⁴³ See Clinical Study Report, OB-302 11/1/2007 – 5/19/09

increasing maternal age. There has been no evidence that it is due to parental behavior (other than age) or environmental factors.

Sponsor's Proposed Qnexa® Pregnancy, Labor and Delivery, and Nursing Mothers Labeling:

Reviewer Comment:

The MHT will provide a thorough in-depth review of the Sponsor's proposed labeling, as well as discussing pertinent information from the DMEP Pharmacology/Toxicology review of the nonclinical data from animal reproductive and developmental toxicity studies, in an addendum to this review, at a later date.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- The use of QNEXA during pregnancy is not recommended. Women of childbearing potential should use adequate contraception while taking QNEXA. (5.2)

-----USE IN SPECIFIC POPULATIONS-----

- The safety and effectiveness of QNEXA has not been studied in pregnant women. (8.1)

5.2 Precautions Pregnancy

Topiramate, one of the components of QNEXA, has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies (see USE IN SPECIFIC POPULATIONS). QNEXA has not been studied in pregnant women, therefore, the use of QNEXA during pregnancy is not recommended. Women of childbearing potential should use adequate contraception while taking QNEXA. Weight loss may increase fertility. Patients should be advised to notify their physician and discontinue treatment with QNEXA if they become pregnant.

7 DRUG INTERACTIONS

7.1 Studies Evaluating the Effects of QNEXA on Other Drugs

Oral Contraceptives: Co-administration of multiple once-daily doses of QNEXA (15/92 mg) with a single oral contraceptive dose containing 35 µg ethinyl estradiol and 1 mg norethindrone decreased the AUC_{0-inf} of ethinyl estradiol by 16% and increased the C_{max} and AUC_{0-inf} of norethindrone by 22% and 16%, respectively. The possibility of decreased contraceptive efficacy should be considered in women of child-bearing potential taking QNEXA concomitantly with oral contraceptive products containing estrogen (see **PRECAUTIONS**).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy: Pregnancy Category C

No studies have been conducted using QNEXA in pregnant women. The use of QNEXA during pregnancy is not recommended. Women of child-bearing potential should employ adequate contraception while taking QNEXA. Fertility may increase as a result of weight loss. Patients should be advised to notify their physician and discontinue treatment with QNEXA if they become pregnant (see PRECAUTIONS).

In embryo-fetal toxicity studies conducted by VIVUS, neither phentermine alone (3.75 mg/kg/day), nor topiramate alone (25 mg/kg/day), or combination (3.75/25 mg/kg/day) was teratogenic in rats. On a mg/m² basis, the dose levels of phentermine and topiramate evaluated in this study represent approximately 6 times the amounts of phentermine and topiramate contained in the recommended dose of QNEXA and approximately 3 times the amounts of phentermine and topiramate contained in the maximum dose of QNEXA. On a mg/m² basis, this dose represents up to 6.5 times the amounts of phentermine and topiramate present in either the recommended or maximum recommended doses of QNEXA.

In rabbits, no teratogenic effects were associated with administration of either phentermine as a single agent or phentermine and topiramate as a fixed-dose combination. A slight increase in the incidence of rib and/or vertebral defects was noted in fetuses from topiramate-alone treated dams. On a mg/m² basis, the topiramate and phentermine doses that were tested in rabbits are up to 13 times the amounts of phentermine and topiramate present in either the recommended or maximum recommended doses of QNEXA.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. Formal embryo-fetal development studies on phentermine, another component of QNEXA have not been conducted.

Collectively, these results suggest that co-administration of phentermine and topiramate to pregnant rats and rabbits during the period of organogenesis was not associated with teratogenic effects.

Reviewer Comment:

The Sponsor proposes a pregnancy category C drug classification, but provides warnings and precautions consistent with a pregnancy category D or X drug. A Pregnancy Category C designation does not routinely trigger labeling language in Warnings and Precautions or Contraindications [see 21 CFR 201.57(c)(9)(i)(A)(3)].

8.2 Labor and Delivery

The effect of QNEXA on labor and delivery in humans is unknown. In studies of rats where dams were allowed to deliver pups naturally, no topiramate drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day.

8.3 Nursing Mothers

Topiramate is excreted in human milk. QNEXA is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

DISCUSSION AND CONCLUSIONS

Obesity and Pregnancy

Obesity presents a significant public health problem in the U.S. with a rapid increase in obesity prevalence in the last two decades. In 2007 - 2008, the prevalence of obesity in U.S. women was 35.5%.⁴⁴ In 2003 – 2004, approximately 30% of U.S. women ages 20 - 39 years were obese based on data from the National Health and Nutrition Examination Survey.⁴⁵ Obesity has a negative impact on a woman's reproductive health including polycystic ovarian syndrome, menstrual irregularities, difficulty conceiving, and a possible higher risk for repetitive early spontaneous abortions.⁴⁶ Pre-pregnancy obesity may be associated with an increased risk of major malformations including neural tube defects, omphaloceles, heart defects, and orofacial clefts. The mechanism for this association between obesity and observed malformations is not known but may be related to severe metabolic and hormonal alterations including hyperglycemia, elevated insulin levels, and elevated estrogen levels; diabetes; and/or nutritional deficits from dieting or poor quality diets.⁴⁷ Despite the potential adverse maternal and fetal outcomes associated with obesity during pregnancy, weight loss should occur prior to a pregnancy, not during one. A minimum weight gain, and no weight loss is recommended during pregnancy for women who are already overweight or obese, because of the obligatory weight gain that occurs in maternal tissues (the uterus, breasts, blood volume, and in the fetal-placental unit) during pregnancy. Metabolic alterations, including insulin resistance, occur in pregnancy and these alterations are an adaptive response to allow a more efficient transfer of fuels across the placenta to the fetus. Because of the metabolic alterations that occur during pregnancy, pregnant women have an increased risk for ketonuria and ketonemia, especially with an inadequate food intake. Concerns exist regarding the metabolic consequences of weight loss in pregnancy and neurodevelopmental outcomes in childhood, especially the possibility of ketonemia leading to suboptimal neurologic development.⁴⁸ In addition, inadequate nutrition reaching the fetus can lead to intrauterine growth retardation and prematurity.

Pregnancy Category Classification

Choice of pregnancy category and inclusion of required risk statements are defined by the current labeling regulations at 21 CFR 201.57. Each category is defined by the availability of and findings from reproductive and developmental toxicity studies in animals and studies of drug use during human pregnancy. The pregnancy category definitions for pregnancy categories C, D, and X include a required consideration of both the potential risks and benefits of maternal drug use during pregnancy. The acceptability of clinical benefit to a woman for using a drug for

⁴⁴ Flegal K, Carroll M, et al. Prevalence and trends in obesity in US adult, 1999-2008. JAMA 2010 Jan;303(3):235-41

⁴⁵ Ogden C, Carroll M, et al. Prevalence of overweight and obesity in the US, 1999-2004. JAMA 2006;295:1549-55

⁴⁶ Brown K, Apuzzia J, Weiss G. Maternal obesity and associated reproductive consequences. Women's health 2010; 6(2):197-203

⁴⁷ Watkins M, Rasmussen S, et al. Maternal obesity and the risk for birth defects. Pediatrics 2003; 111:1152-58

⁴⁸ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: <http://nap.edu/catalog/12584.htm>

a particular indication during pregnancy is weighed against the known and potential embryo and fetal drug risks.

While not usually the case, drug products can have different pregnancy category classifications for different indications. An example of this is the product Zoladex[®] (goserelin acetate).⁴⁹ Zoladex[®] has a pregnancy category D classification for use in advanced breast cancer and a pregnancy category X classification for use in endometriosis. In advanced breast cancer, the benefits of maternal drug treatment may outweigh the risks of fetal drug exposure as ultimately, the survival of the fetus depends on the survival of the mother. Drug products can also have different pregnancy category classifications depending on the trimester of use. ACE Inhibitor products⁵⁰ are classified as pregnancy category C for first trimester use and pregnancy category D for second and third trimester use.

Qnexa (phentermine/topiramate) Controlled Release Capsules is a combination drug product that contains immediate-release phentermine hydrochloride beads and modified-release topiramate beads. As a single ingredient drug, phentermine (marketed as Adipex-P) is an appetite suppressant and the most commonly prescribed drug for weight loss in obesity treatment in the United States. Phentermine, a DESI drug, was classified as a pregnancy category C drug because of a lack of both animal and human data during pregnancy. Since phentermine approval, limited human data have shown no increase in congenital malformations; however, use is generally avoided during pregnancy because of concerns about the effects of weight loss on embryo-fetal development.⁵¹ In addition, phentermine has pharmacologic activity similar to amphetamines, and concerns exist regarding the effects of amphetamine-induced vasoconstriction on mother, placenta, and fetus. Studies in pregnant sheep demonstrate that methamphetamine administration decreases both uterine and umbilical blood flow with methamphetamine.⁵²

Reviewer Comment:

The MHT has never had the opportunity to review phentermine pregnancy labeling. If phentermine were under review at this time, it is likely that the MHT would recommend a pregnancy category X classification (contraindication) for the drug based on the potential fetal risks based on drug mechanism of action and no acceptable clinical benefit to a woman during pregnancy for the indicated use.

Topiramate, an anti-epileptic drug (AED) that is also approved for migraine prophylaxis, is currently used off-label for weight loss. Topiramate was classified as a pregnancy category C drug based on animal teratogenicity and embryotoxicity observed at clinically relevant doses and clinical benefit of maternal treatment during pregnancy for both indicated uses. Limited data on human exposure have shown a possible increased risk in major malformations (cleft palate), a finding that is consistent with animal findings. In addition, the pregnancy subsection of topiramate labeling was recently revised to include information on topiramate-induced metabolic acidosis in pregnancy and the association of metabolic acidosis with fetal harm. Both seizures

⁴⁹ See Zoladex labeling

⁵⁰ See Zestril labeling

⁵¹ See REPROTOX[®]. Available through MicroMedex

⁵² See REPROTOX[®]. Available through MicroMedex

and migraine headaches can lead to adverse pregnancy outcomes if not appropriately treated and controlled during a pregnancy. Seizures are associated with an increased risk for low birth weight infants, preterm delivery and infants who are small for gestational age.⁵³ Migraine is a risk factor for hypertensive disorders, including pre-eclampsia, in pregnancy,⁵⁴ and may lead to vascular complications, including stroke, during pregnancy.⁵⁵ Migraines during pregnancy are also associated with an increased risk for low birth weight infants, preterm delivery, and delivery via caesarian section.⁵⁶

Based on the positive animal data from reproductive and developmental toxicology studies conducted with Qnexa and topiramate, a pregnancy category C or X classification⁵⁷ could be considered for Qnexa. However, when considering the potential risks of the drug when used during pregnancy versus the potential benefits of Qnexa for the treatment of obesity, a pregnancy category X classification is appropriate because, as described earlier, a minimum weight gain (and no weight loss) should occur during pregnancy. There is potential fetal risk and no acceptable clinical benefit for using Qnexa in pregnancy.

Pregnancy Prevention

Drug products that are likely to be used in women of childbearing potential and that have a pregnancy category D or X classification should have accompanying pregnancy prevention recommendations or strategies in place. Pregnancy prevention measures can range from recommendations placed in labeling, to a stringent risk mitigation program with requirements for elements to assure safe use of a drug product. As previously mentioned, the selection of a particular pregnancy prevention strategy is generally based on a drug's indication(s), likely use in women of childbearing potential, and risk/benefit considerations of a drug if used during pregnancy. Because there is the potential for adverse pregnancy outcomes and no clinical benefits for a woman to use Qnexa during a pregnancy, the MHT recommends that pregnancy prevention recommendations be included in labeling. In addition, pregnancy prevention should be a goal of the Qnexa Risk Evaluation and Mitigation Strategy (REMS). The Medication Guide for patients, would be an appropriate tool to use for pregnancy prevention and related pertinent information and recommendations at this time. Stringent risk mitigation pregnancy prevention programs are generally reserved for drug products with demonstrated teratogenicity in humans or highly suspected teratogenicity in humans. Topiramate has demonstrated selective animal teratogenicity and embryotoxicity at clinically relevant doses, and limited human data have shown a possible increased risk in major malformations (cleft palate); however, no pregnancy prevention measures are in place for topiramate. Phentermine has not demonstrated a signal for teratogenicity. A stringent pregnancy prevention risk mitigation program would probably be ineffective for Qnexa, as such a program would likely drive drug use to the already-approved individual products, phentermine and topiramate, and topiramate is not labeled for the treatment

⁵³ Chen YH, Chiou HY, Li HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. *Arch Neurol*, 2009;66(8):979-84

⁵⁴ Faccinetti F, Allais G, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. *Cephalalgia*, 2008;29:286-92

⁵⁵ Bushness C, Jamison M, James A. Migraines during pregnancy linked to stroke and vascular diseases: US population based case-control study. *BMJ* 2009;338

⁵⁶ Chen HM, Chen SF, et al. Increased risk of adverse pregnancy outcomes for women with migraines: a nationwide population-based study. *Cephalalgia*, 2009 Jul 9

⁵⁷ See Appendix A, FDA Pregnancy Category definitions

of obesity. This would lead to obesity treatment in women of childbearing potential with drug labeling that does not optimally inform safe and effective use of the drug combination.

The success of pregnancy prevention recommendations or requirements ultimately depends on patient compliance with the use of effective contraception. In order to influence and reinforce contraceptive compliance, one must understand the contraceptive behaviors of their population. A better understanding of the benefits and obstacles of different contraception types used by overweight and obese women is needed to appropriately inform Qnexa labeling with recommendations of effective contraception.⁵⁸ Obesity itself presents contraceptive challenges. Conflicting data exist on the effects of obesity and the efficacy of contraception, especially on the efficacy of hormonal contraceptives. Disease co-morbidities and the risk for venous thromboembolism are higher in obese women and may preclude the use of hormonal contraceptives in some of these women.⁵⁹ In addition, Qnexa may impact oral contraceptive efficacy as stated in the proposed Qnexa labeling in Drug Interactions.⁶⁰ Barrier methods, such as a diaphragm, may be difficult for an obese woman to insert (and resizing is needed with weight gain or loss). The use of condoms requires partner participation and consent. Use of an Intrauterine Device (IUD) requires insertion by a skilled medical practitioner. In addition, weight loss in overweight and obese woman may increase fertility; thereby, increasing the chance for pregnancy. In order to address these concerns and include effective contraception recommendations in labeling, information is needed both on effective contraception methods and types of contraception methods that are acceptable to, and appropriate for women who will use Qnexa for the treatment of obesity. Information on effective and acceptable methods of contraception for overweight and obese women of childbearing potential will be crucial for the success of pregnancy prevention with Qnexa use.

Pregnancy Exposure Registry

Pregnancies will likely occur with Qnexa treatment, even with carefully designed pregnancy prevention and risk mitigation strategies. Thirty-four pregnancies occurred in the Qnexa clinical development program, despite a requirement for the use of two forms of contraception. Information should be collected on Qnexa exposure during pregnancy in order to provide clinically relevant human data to inform labeling. A drug-based pregnancy exposure registry (a prospective observational cohort study)⁶¹ would be the appropriate mechanism to use to collect Qnexa pregnancy exposure data.

A prospective observational cohort study collects information on drug exposure during pregnancy and associated pregnancy and infant outcomes. Enrollment is based on known drug exposure but occurs before pregnancy outcome is known and, data are actively collected from enrolled women and/or from their healthcare providers. In addition, a prospective observational cohort study can: detect an increased risk for some adverse developmental outcomes; provide margins of reassurance regarding lack of risk; monitor for suspected risks raised by nonclinical studies, premarketing clinical studies, or postmarketing case reports; and provide data on factors

⁵⁸ Schraudenbach a, McFall A. Contraceptive use and contraception type in women by body mass index category. *Women's Health Issues* 2009 (19):381-89; www.whjournal.com

⁵⁹ Murthy AS. Obesity and contraception: emerging issues. *Semin Reprod Med.* 2010 Mar;28(2):156-63

⁶⁰ See draft Qnexa labeling submitted December 28, 2009

⁶¹ See Guidance for Industry: Establishing Pregnancy Exposure Registries, August 2002

that affect the risk of adverse outcomes. Qnexa should have its own pregnancy exposure registry to collect pregnancy exposure data and should not be included in the existing North American Antiepileptic Drug (AED) Pregnancy Registry. The North American Antiepileptic Drug (AED) collects information only on major malformations with AED use, and Qnexa contains two active ingredients, an AED (topiramate) and a non-AED (phentermine). Phentermine has pharmacologic activity similar to amphetamines, and amphetamine use during pregnancy is associated with teratogenicity, intrauterine growth retardation and prematurity, and adverse neurodevelopmental outcomes.⁶² All pregnancy exposure outcome data, including both maternal and fetal effects should be collected on Qnexa. A pregnancy exposure registry should be included as a Postmarketing Requirement (PMR) for Qnexa upon approval.

Clinical Lactation Trial

A clinical lactation trial should be conducted for Qnexa, because the drug is systemically available and will be used women of childbearing potential, including lactating women. Adequate information is not available regarding the drug's concentration in milk and the estimated infant daily dose of drug available through human milk. Limited human lactation data is available for topiramate show that infant plasma topiramate levels are 10-20% of the maternal plasma level.⁶³ No human lactation data are available for phentermine; however, because phentermine has pharmacologic properties similar to amphetamines, current labeling recommends against human milk feeding. The American Academy of Pediatrics (AAP) Committee on Drugs' statement on "The Transfer of Drugs and Other Chemicals Into Human Milk" states that amphetamines (when used as a drug of abuse) should not be used while nursing because of adverse effects to the infant. The AAP lists other stimulants as drugs that should be used in nursing mothers with caution because of potential infant adverse effects and the unknown effect on infant neurologic development.⁶⁴

A milk-only lactation trial (without infant sampling)⁶⁵ could provide information on the concentration of both components of Qnexa, phentermine and topiramate, in human milk and the calculated daily infant dose from human milk exposure for both components. A clinical lactation trial should be included as a Postmarketing Requirement (PMR) for Qnexa upon approval. The data obtained from a clinical lactation trial should be added to Qnexa labeling in a timely manner in order to appropriately inform drug use and risk/benefit decision making during lactation.

Labeling

Vivus, Inc. proposed Qnexa labeling that could be confusing to clinicians and female patient of childbearing potential. The Sponsor proposes a pregnancy category C drug classification, but includes pregnancy warnings and precautions that are typically associated with a pregnancy

⁶² Plessinger M. Prenatal exposure to amphetamines: risks and adverse outcomes in pregnancy. *Ob Gyn Clinics of NA*. 1998 Mar; 25(1):119-138

⁶³ See current approved Topamax labeling, December 22, 2009

⁶⁴ American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. 2001 Sep; 108(3):776-89

⁶⁵ See *Draft Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, February 2005*. This draft guidance has been revised based on public comments, Advisory Committee Meeting (2007) recommendations and current scientific thinking and is in clearance for final publishing.

category D or X drug.⁶⁶ A Pregnancy Category C designation does not routinely trigger labeling language in Warnings and Precautions or Contraindications [see 21 CFR 201.57(c)(9)(i)(A)(3)]. More importantly, a pregnancy category C designation does not properly reflect the benefit/risk balance for Qnexa based on all available data for the combination drug product or its individual components.

Based on its indication for use and available data, Qnexa labeling should include:

- A contraindication for use in pregnancy
- A warning and precaution for females of childbearing potential that includes recommendations for pregnancy testing prior to starting Qnexa
- Use of effective contraception during Qnexa treatment (along with types of effective contraceptive methods)
- The importance of stopping Qnexa immediately if a pregnancy is suspected or confirmed
- The importance of undertaking a weight loss program prior to planning a pregnancy (not during pregnancy)
- Information about the potential increase in fertility with weight loss in an overweight or obese woman.

In addition, appropriate information should be placed in the pregnancy and nursing mothers subsections of labeling to adequately inform prescribing decisions.

RECOMMENDATIONS

The Maternal Health Team (MHT) has the following recommendations for Qnexa:

1. Pregnancy Category Classification

Contraindicate Qnexa for use in pregnancy (pregnancy category X classification). Studies in animals with topiramate have demonstrated adverse fetal outcomes and pregnant woman should not lose weight. There are potential risks and no acceptable clinical benefits for a woman using Qnexa in pregnancy.

2. Pregnancy Prevention

Require that the Qnexa Risk Evaluation Mitigation and Strategy (REMS) have a goal for pregnancy prevention. Qnexa labeling, including the Medication Guide should include the following pregnancy prevention messages and information for clinicians and females of childbearing potential:

- Qnexa use in pregnancy is contraindicated
- Pregnancy testing is needed prior to initiating therapy
- Use effective and acceptable contraception during therapy
- Stop Qnexa immediately if a pregnancy is suspected or confirmed
- Weight loss in overweight and obese women may potentially increase fertility
- The importance of undertaking a weight loss program before planning a pregnancy or becoming pregnant rather than during a pregnancy.

⁶⁶ See Appendix A for FDA pregnancy Category Definitions

The Sponsor should provide information on effective contraception methods and types of contraception methods that are acceptable to, and appropriate for, females of childbearing potential who will be using Qnexa for the treatment of obesity. This information is vital to informing labeling because of the Qnexa drug-drug interaction with oral contraceptives and the need for information on the benefits and obstacles of different contraception types used by overweight and obese women.

3. Pregnancy Exposure Registry - A Prospective Observational Cohort Study

Require the Sponsor to conduct a pregnancy registry (a prospective observational cohort study) as a Postmarketing Requirement (PMR). The Sponsor should submit their protocol for review and comment, prior to starting the study.

4. Clinical Lactation Trial

Require the Sponsor to conduct a milk-only lactation trial (without infant sampling) as a Postmarketing Requirement (PMR) to provide information on the concentration of both phentermine and topiramate in human milk and the calculated daily infant dose from human milk exposure for both drugs. The Sponsor should submit their protocol for review and comment prior to starting this trial. [The Maternal Health Team can share language with the division (and the sponsor) regarding our current thinking on clinical lactation trial design and requirements.]

5. Labeling

The MHT will provide pregnancy, nursing mothers, and information for females of childbearing potential labeling recommendations for Qnexa as an addendum to this review at a later date. Labeling will be done in collaboration with the DMEP Qnexa Pharmacology/Toxicology Reviewers.

APPENDIX A:
FDA Pregnancy Category Definitions

Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)	
Category	Definition
A	Adequate and well-controlled (AWC) studies 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).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
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 the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
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 a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

CONSULTATION REVIEW

NDA 22580 (505B2)

Drug: Qnexa (phentermine + topiramate)

Sponsor: Vivus, Inc

Indication: Anti- obesity (Combination centrally acting appetite suppressant)

Request for consultation from: Pat Madara, DMEP White Oak, bldg 22

Date of the request: March 10, 2010

Subject of consultation: A consult request “for adverse pregnancy outcomes in AERS database such as congenital anomalies associated with the use of topiramate and phentermine separately and co-administered”.

Reviewer: Sonia Tabacova, MD, Ph.D.

Division: Psychiatry Products

Review date: May 26, 2010

Phentermine (schedule IV): sympathomimetic amine, action is thought to be via norepinephrine reuptake inhibition and inhibition of monoamine oxidase subpart A activity; currently approved for short-term weight loss;

Topiramate: sulfamate-substituted monosaccharide that is believed to block voltage dependent sodium channels, augment the activity of gamma-aminobutyrate at GABA-A receptors, antagonize the AMPA/kinase subtype of the glutamate receptor, and inhibit the carbonic anhydrase enzyme. Weight loss is via an unknown mechanism.

Adverse developmental events reported to FDAs AERS in association with topiramate and phentermine gestational exposures

Topiramate (Topamax)

A total of 115 spontaneous reports of adverse fetal, neonatal and/or postnatal events associated with administration of topamax as a monotherapy to pregnant women were retrieved from FDA’s Adverse Event Reporting System (AERS) by Dr. Ana Szarfman. Out of these, 39 reports were excluded from this review because of the following reasons: duplicate reports (n=25); irrelevant reports (topiramate exposures not gestational/prenatal) (n=13); and outcome of pregnancy not reported (n=1). The remaining 76 case reports are the subject of this review.

Reporting sources: Out of the reviewed 76 reports, 23 originated in the U.S.; the majority (56, or about 70%) were from other countries. About a third of all reports (22 of 76) were from literature sources. Most of the reports (62 of 76, or over 80%) were from health professionals that supports their credibility.

The reported adverse events took place over the period from 1997 through 2009 (incl.)

Indication: Information about topamax indication was available in 51 reports. In 92% of these (47 of 51) topamax was used in pregnancy for treatment of maternal epilepsy; in only 4 cases the indication was migraine in pregnancy. No concurrent maternal diseases were reported except for 3 cases of pregnancy complications (premature rupture of membranes; amnionitis) and 1 case of pre-existing disease (brain tumor, surgically removed before conception). Thus, in the majority of cases there was uniformity of the maternal health background.

Administration and doses: Generally, topamax was administered as a monotherapy. Concomitant medication with other drugs was reported in only 5% of the cases (4 of 76), including: carbamazepine (in 2 cases, both during the 1st trimester); lamotrigine (in 1

case, prior to the pregnancy); and chemotherapy/radiation therapy (in 1 case, 2 months before conception).

Topamax dose was reported in 45 of 76 cases. In the majority of these (29 of 45), the doses were less or equal to 200 mg/day (in 64% of cases); > 200 to 400 mg/day in 9 cases (20%); > 400 to 600 mg/day – in 4 cases (9%), and over 600 mg/day – in 3 cases (7%). Information about timing and duration of topamax administration in pregnancy was available in 46 reports. In most of these cases (40 of 46, or 87%) the exposure involved the 1st trimester of pregnancy (the period of major organogenesis), and in more than a half of them (21 of 40) topamax administration continued through the entire duration of pregnancy. Exposures starting after the 1st trimester were not common (6 of 46, or 13%). This indicates that in the prevailing majority (87%) of adverse event reports topamax administration involved the most vulnerable period of embryofetal development, the 1st trimester of gestation.

Maternal characteristics were poorly reported; i.e., maternal age was reported in less than a third of the cases (21 of 76), and information about gravidity and parity was available in less than one sixth of the reports (13 of 76). According to these limited data, maternal age between 20 and 30 years was prevalent (in 14 of 21 cases); the proportion of primigravida and primipara was one third, and about one half of mothers were multiparous (3 or more births). Smoking in pregnancy was reported in 6 cases, alcohol consumption – in 5 cases (in 3 of these combined with smoking), and drug use (cannabis) – in 1 case.

Pregnancy outcome information was available in most of the reports (70 of 76). Elective abortions due to fetal malformations comprised 13% of the reported outcomes (9 of 70). The rest of the outcomes were live births (61, or 87%). Gestational age at birth was reported in less than a half of these (27 births), including 19 term- and 8 preterm births. Neonatal gender (reported in 46 cases) was 56% males (26 of 46) and 44% females (20 of 46).

Adverse developmental events

- **Congenital malformations** were reported in 93% of all AE reports (71 of 76). The remaining 7% (5 of 76) reported postnatal adverse events without structural malformations. Thus, congenital malformations were almost exclusively the reason for adverse event reporting in association with topamax use in pregnancy.

Reported cases of adverse events

Number of all AE cases: 76

Adverse events	N reported/ Per cent of all AE reports
Congenital malformations:	71 (93.4%)
- Non genetic	67
- Genetic syndromes	4
Postnatal AE* (no malformations)	5 (6.6%)

* Developmental delays (2), Convulsions (1), Strabismus (1), Hypotonia, feeding difficulties (1)

The reported 71 cases of congenital malformations included 4 cases of malformation syndromes of genetic origin all confirmed by karyotype analyses: Edward's syndrome (Trisomy18); Di George's (chromosome 22 q11.2 deletion syndrome, also known as conotruncal anomaly face syndrome, congenital thymic aplasia); Cri-du-chat (also known

as chromosome 5p deletion syndrome); Prader-Willi (chromosome 15 q11-13 deletion syndrome that involves obesity, decreased muscle tone, decreased mental capacity, and hypogonadism). These were excluded from our further review since genetic birth defects could arise independently of prenatal drug exposures. Out of the remaining 67 cases, 3 did not specify the type of malformations. Thus, the following description of the reported malformations was based on 64 case reports (see the following table).

Congenital malformations' spectrum and reporting frequency

Type of malformation	N reported (Per cent of all malformation cases)*
Total reported malformation cases	67 (excluding congenital genetic syndromes)
- Malformations not specified	3
- Malformations specified	64
Craniofacial	21 /64 (32.8%)
- Cleft lip and/or palate	11
- Facial dysmorphism (incl. auricular dysplasia)	6
- Micrognathia	4
- Skull deformation and ossification abnormalities	3
- Macroglossia	1
Skeletal	19 /64 (29.9%)
- Limb malformations	16
Phalangeal (brachydactyly, adactyly, syndactyly)	8
Long bones (radius, femur hypoplasia, deformity)	5
Hip dysplasia, Talipes	6
Vertebral	4
Cardiovascular	15 /64 (23.4%)
- Ventricular or atrial septal defect	11
- Single ventricle	1
- Patent ductus arteriosus	1
- Pulmonary artery stenosis	1
- Aortic hypoplasia	1
- Aortic valve bicuspid	1
- Transposition of great arteries	1
Genito-urinary	9/ 64 (14.1%)
- Hypospadias	4
- Labia pudenda adhesions	2
- Ureteral malformation (double ureter)	1
- Hydronephrosis	1
- Nephrolithiasis	1
CNS	8/ 64 (12.5%)
- Spina bifida	3
- Microcephaly	1
- Hydrocephaly	1
- Microgyria	1
- Corpus callosum aplasia	1
- Syringomyelia	1
Gastro-intestinal	3/ 64 (4.7%)
- Hernia (diaphragmatic, umbilical, inguinal)	3
Neoplasia (hemangioma, glioma)	2 /64 (3.2 %)
Pulmonary	1/ 64 (1.6%)

*Individual per cent values add to more than 100% because of multiple malformation cases

The reported malformations displayed a distinctive and consistent pattern. Dominating among the reported congenital birth defects were craniofacial malformations (predominantly oral clefts, but also facial and skull dysmorphism, micrognathia), as well as skeletal limb defects (long bones' and phalangeal hypoplasia, aplasia or deformities, including adactyly, brachydactyly, syndactyly, radius or femoral hypoplasia, hip dysplasia, talipes). Both craniofacial and skeletal limb malformations were each reported in about 30% of the reviewed 64 malformation reports. Cardiovascular (predominantly ventricular or atrial septal defects) were the third frequently reported group of malformations (23% of reports). The reporting rate of these defects was not higher in the premature births (1 of 8), or in the low body weight infants (1 of 14), which suggests that they cannot be attributed to neonatal immaturity. Less frequently reported (in 14% of the reports) were genitourinary abnormalities (hypospadias, labial adhesions, ureteral malformations, hydronephrosis, congenital nephrolithiasis) and CNS malformations in 12% of reports (neural tube closure defects, i.e., spina bifida, and brain hypoplastic or aplastic lesions, i.e., microcephaly, microgyria, corpus callosum aplasia, hydrocephaly). Gastrointestinal and pulmonary malformations were rarely reported (single cases).

Note: It is of note that an uncommon abnormality – i.e., congenital nephrolithiasis, was reported in association with topiramate prenatal exposure. That it was likely for this association to be causal is supported by the ability of topiramate, as a carbonic anhydrase inhibitor to “create a physiological environment that increases the risk of renal stone formation” (*From Topiramate labeling, under “Other Drug Interactions”*).

Multiple malformations involving combinations of the above defects were reported in about 20% of the cases (13 of 64). The most frequently reported combination (in nearly half of the multiple malformation cases) included skeletal (limb) malformations plus cardiovascular and craniofacial defects (6 of 13).

This malformation pattern is similar to the types of malformations seen in topiramate developmental toxicity studies in experimental animal species (as shown in Topiramate labeling reproduced below).

“Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD=400 mg/day) on a mg/m² basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m² basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m² basis). Clinical signs of maternal toxicity were seen at

400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m² basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.” (From Topiramate labeling, under “Pregnancy”)

- Adverse outcomes other than congenital malformations:

Intrauterine growth retardation was reported in addition to other pathology in 14 of 61 live births. It was not reported as an independent adverse event.

Postnatal adverse events were reported in 9 of 61 live births. In 5 of these 9 cases there were no congenital malformations; the reported events included mental and physical developmental delays (in 2 cases, one of which also involved maternal use of cannabis during pregnancy); convulsions (infantile spasms, or West’s syndrome) in 1 case; muscle hypotonia and feeding difficulties (1 case); and strabismus (1 case). In the remaining 4 cases, postnatal adverse events arose in association with accompanying congenital malformations. These cases included 2 cases of mental and physical developmental delays with accompanying CNS or cardiovascular malformations and 2 cases of infant deaths (one case of intra-partum death from cardiac and pulmonary complications in a premature infant with multiple malformations; and one death during the 1st week of life in an infant with a major cardiovascular malformation (one ventricle) whose mother had been treated with another antiepileptic drug, lamotrigine, prior to pregnancy and prior to topiramate.

Topiramate gestational exposure in different AE’s – time, duration and dose

In nearly all congenital malformations cases, topiramate gestational exposure (data available in 42 cases) started in the 1st trimester of pregnancy (37 of 42, or 88%), and, in half of these, did not continue beyond the 1st trimester. In all cases of postnatal AEs, topiramate administration covered the entire pregnancy, in some cases continuing even beyond birth through lactation. It is of note that the only case in which topiramate administration started late in gestation (in the 3rd trimester) presented with hypotonia and feeding difficulties (i.e., clinical signs attributable to the pharmacological effect of the drug), but no other pathology.

Thus, the data suggest that structural congenital malformations were associated with topiramate exposures involving the 1st trimester of pregnancy, while postnatal CNS manifestations and developmental delays were associated with exposures that continued beyond the 1st trimester.

Topamax dose (in the reported dose range of <200 - >600 mg/day) did not appear to affect the type of AEs or the rate of their reporting. The adverse events reported at daily doses of 200 mg or less were not different by type and reporting frequency from those at daily doses of over 200 or over 400 mg. However, the small number of cases treated with doses greater than 400 mg/day (n=7) do not allow a definitive conclusion.

Confounding factors:

- Concomitant drug use was reported in only 4 cases: 2 involving carbamazepine (1st trimester), 1 – lamotrigine prior to pregnancy, and 1 – chemo- and radiation therapy 2 months before conception. The types of malformations reported in these cases (i.e., hemangioma and diaphragmatic hernia in the 2 carbamazepine cases; a single heart ventricle in the lamotrigine case; and a genetic malformation syndrome Cri du chat in the pre-pregnancy chemo-and radiation exposure) were different from the malformation pattern seen with topiramate alone.
- Smoking, alcohol consumption and recreational drug use were rarely reported (in 6, 5 and 1 case, respectively). The types of malformations reported in these particular cases were not different from the rest of the reported cases.
- Maternal demographic characteristics (age, gravidity, parity) were reported in insufficient number of reports to allow for a meaningful interpretation.
- Gestational age at birth could confound topamax association with cardiovascular malformations since cardiac septal defects are known to be more common among immature or pre-term infants. The present case series included 8 premature births (37 weeks gestation or less) and 14 cases of intrauterine growth retardation or small for gestational age babies. In these cases, cardiovascular malformations were not seen more frequently than in the rest of the cases (i.e., 1 case of atrial septal defect in 8 AE reports in premature infants; and 2 cases - of atrial and of a ventricular septal defect in 14 AE reports of intrauterine growth retardation and small for gestational age infants, as compared to 15 cardiovascular malformations in the total of 76 AE cases reviewed).

Conclusions:

- The adverse events that have been reported to FDA in association with prenatal exposures to topiramate since 1997 up to the present are almost exclusively congenital malformations; elective abortions due to congenital malformations constitute 13% of the AE reports.
- Over 80% of these AE reports were made by health professionals that is in favor of their credibility;
- The reported malformations display a distinctive and consistent pattern. Dominating are craniofacial malformations (predominantly oral clefts) and skeletal limb defects (long bones and phalangeal), followed by cardiovascular malformations (predominantly ventricular and/or atrial septal defects). The combination of skeletal, craniofacial and cardiovascular malformations is the most frequently reported combination in the multiple malformation cases.
- The presence of a pattern in the reported congenital malformations and their similarity to those seen in experimental animals prenatally exposed to topiramate indicates that the reported malformations in humans are not random and their association with maternal exposure to topiramate during gestation is plausible.

This conclusion is further supported by:

- The use of topiramate as a monotherapy in nearly all reported malformation cases;
- The uniformity of the maternal background health status (i.e., uniformity of the indication, epilepsy, in more than 90% of the reported cases and no reported concurrent disease or pregnancy complication);

- The time and duration of the prenatal topiramate exposure, involving in the great majority of cases the 1st trimester of gestation, the period of major organogenesis, most susceptible to induction of malformations.

Reviewer's note: The inferences of this review are not to be interpreted as a proof or rejection of exposure-effect *causal* relationship. Observational case studies – as this one - by definition can not provide a proof of causality since they are based on AE reports, there is no control group, and it is not possible to determine the incidence of the adverse events (no denominator). Thus, our conclusions are to be used as a suggestion *supporting* the presence or absence of a causal relationship. Some of the Hill's causality criteria are met in our review of this AE set, i.e., consistency, plausibility, temporality.

Phentermine

A total of 15 spontaneous reports of adverse fetal, neonatal and/or postnatal events associated with administration of phentermine to pregnant women were retrieved from FDA's AERS. Out of these, 4 reports were excluded from this review: 3 duplicate reports and 1 irrelevant report (exposure not gestational/ prenatal). The remaining 11 case reports are the subject of this review.

Reporting sources: All of the reviewed 11 AE reports originated in the U.S.; most of the reports (6 of 11) were from non- health professionals. The reported adverse events took place over the period from 1985 through 2001. It is noteworthy that during the long time period since 1985, a very small number of AE reports associated with phentermine gestational exposures have been submitted.

Indication: Information about phentermine indication was available in 7 reports; in all these cases the indication was weight loss.

Administration and doses: Concomitant medication with other drugs was reported in only 1 case (fenfluramine, simultaneously with phentermine).

Phentermine dose was reported in only 3 cases (30 or 37.5 mg/day); in 1 case, only one dose was administered (dose not specified). The timing of administration in pregnancy (available in 10 reports) was during the 1st trimester in all cases. The duration of administration in most cases (8 of 10) was less or up to than 1 month (in 2 of these, the duration was 1 and 5 days); none of the cases were exposed throughout pregnancy – the longest exposure was 4-5 months.

Maternal characteristics were not reported.

Pregnancy outcome: In 10 of 11 cases, the outcome was a live birth; one case of congenital heart disease died during labor. Gestational age at birth was reported in 6 cases, including 3 term- and 3 preterm births. Neonatal gender (reported in 9 cases) was 4 males and 5 females.

Adverse developmental events

Congenital malformations were reported in 10 of 11 AE reports. The remaining 1 case was growth retardation without structural malformations. Half of the malformation cases (5 of 10) were multiple malformations (not otherwise specified in 2 cases).

Out of the 10 cases, 2 did not specify the type of malformations. Thus, the description of the type of reported malformations was based on 8 case reports (see the following table).

Congenital malformations' spectrum

Type of malformation	N reported
Total reported malformation cases	10
- Malformations not specified	2
- Malformations specified	8
Cardiovascular	8
- Heart valve pathology	3
- Ventricular or atrial septal defect	3
- Patent ductus arteriosus	1
- Transposition of great arteries	1
- CV malformation (not specified)	1
Other combined with cardiovascular	2
- Lung agenesis, tracheal stenosis, thymic hypoplasia, cleft palate, gallbladder aplasia, renal dysplasia, atrial septal defect	1
- Genitourinary: abnormal kidneys, bladder outlet obstruction, hydronephrosis, ascites, hypospadias, macroglossia, patent ductus arteriosus	1
Skeletal (only) (reduction deformities of arms , phalangeal aplasia)	1

Postnatal outcomes

Death in 2 of the 10 live births (on postnatal days 1 and 12): in one case of “heart and lung damage” in a preterm infant (phentermine administration during 5 days in the 1st trimester), and in another case of multiple malformations in a preterm infant (phentermine administration during 6 weeks in the 1st trimester).

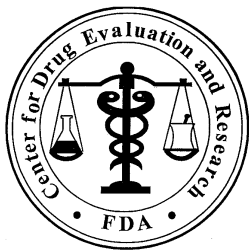
Comments:

The reported malformations are mostly cardiovascular (in 8 of the total of 10 malformation cases). Out of these 8 cases, in 2 the cardiovascular defect was combined with multiple other malformations (see the table).

However, the number of AE reports is very small (a total of 11 AE reports since 1985); and it is unclear if this was due to the low use rate of the drug, or to actual absence of adverse effects.

In some cases the prenatal exposure was very short (i.e., 1 day in one case and 5 days in another). It is unlikely that exposures of this duration could be the reason for the reported multiple major malformations in these cases.

Altogether, the number of the AE reports is too small to draw meaningful conclusions.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 17, 2010

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Subject: AERS Review

Drug Name(s): Phenteramine/Topiramate (Qnexa)

Application Type/Number: NDA 22-580

Applicant/sponsor: Vivus, Inc

OSE RCM #: 2010-500

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1 INTRODUCTION

This review provides an analysis of AERS reports associated with phentermine (Ionamin, Fastin) and topiramate (Topamax). The analysis focuses on reports describing concurrent use of phentermine and topiramate, but also provides an overview of the U.S. serious reports associated with phentermine or topiramate. The Division of Metabolic and Endocrine Products (DMEP) requested this review to assist in their evaluation of NDA 22-580 (Qnexa), a combination product of phentermine and topiramate for the management of weight loss. An Advisory Committee meeting is scheduled for July 15, 2010.

As requested by DMEP, this review excludes reports associated with coadministration of dexfenfluramine or fenfluramine (both withdrawn from the U.S. market in September 1997 because of valvulopathy concerns), and focuses on the following targeted medical event classes: Cardiac, Cognitive, Drug Abuse/Withdrawal, Menstrual, Ophthalmic, Psychiatric, and Psychomotor Disorders.

2 BACKGROUND

This section provides the proposed indication and dosage for phentermine/topiramate (Qnexa) and known safety information for phentermine and topiramate.

2.1 PHENTERMINE/TOPIRAMATE (QNEXA)

Vivus, the sponsor of Qnexa, is seeking an indication for the treatment of obesity, including both weight loss and maintenance of weight loss for obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$), or overweight patients ($\text{BMI} \geq 27 \text{ kg/m}^2$) with weight-related comorbidities. The proposed Qnexa (phentermine/topiramate) dosage forms are 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg, with a recommended dosage of 7.5 mg/46 mg once daily in the morning.

2.2 PHENTERMINE (IONAMIN, FASTIN)¹

Phentermine, a sympathomimetic with pharmacologic activity similar to amphetamine, was initially approved by FDA in 1959 for the short term use (“a few weeks”) in the management of obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$) or overweight patients ($\text{BMI} \geq 27 \text{ kg/m}^2$) with risk factors. The approved dosage is 15 to 30 mg once daily.

Phentermine products were often coprescribed (off label) with dexfenfluramine (Redux) and fenfluramine products (Pondimin) until dexfenfluramine and fenfluramine were removed from the U.S. market in 1997 because of valvulopathy.²

Safety concerns with phentermine center around the 1) dose-related sympathomimetic (both adrenergic and dopaminergic) effects that are primarily cardiovascular (increased blood pressure and heart rate, stroke) and neuropsychiatric (euphoria, insomnia, psychosis), and 2) idiosyncratic reactions such as with overdose or misuse.

The phentermine labeling advises (WARNINGS AND PRECAUTIONS) the following:

- Phentermine is indicated only for short-term (“a few weeks”) monotherapy
- Coadministration of phentermine with other drug products for weight loss (“including selective serotonin reuptake inhibitors”) is not recommended
- Primary pulmonary hypertension (rare, possibility of association with phentermine without coadministration of dexfenfluramine or fenfluramine cannot be ruled out)
- Valvular heart disease (reported in patients who had taken a combination of phentermine with dexfenfluramine or fenfluramine)
- Drug dependence (phentermine is related to amphetamines and other stimulant drugs that have been abused; reports of patients who have increased the dosage to many times that recommended; chronic intoxication can include psychosis)
- Caution in prescribing for patients with even mild hypertension
- Patients with diabetes mellitus may have altered insulin requirements
- Phentermine may decrease the hypotensive effect of adrenergic blocking drugs
- Prescribe and dispense the least amount to minimize the possibility of overdose

Phentermine is CONTRAINDICATED in patients with:

- Advanced arteriosclerosis
- Cardiovascular disease
- Moderate to severe hypertension
- Hyperthyroidism
- Idiosyncrasy to the sympathomimetic amines
- Glaucoma (alpha-adrenoceptor activation can cause mydriasis)
- Agitated states
- A history of drug abuse
- Monoamine oxidase inhibitors (hypertensive crises may result)

AERS

Adverse events associated with phentermine that are frequently reported to AERS (listed in APPENDIX I) are consistent with those described in the phentermine labeling or known pharmacologic effects of phentermine. Of note in the top 25 frequently reported adverse event categories, the leading terms are dysphoria (depression), psychotic disorder, hypertension, arrhythmias, stroke – all possibly associated with phentermine’s inhibition of norepinephrine and dopamine reuptake. Overdose was also frequently reported to AERS.

Phentermine Deaths

AERS contains 14 deaths associated with phentermine that were reported to FDA (marketing through December 31, 1996 (cutoff date chosen because phentermine was coprescribed off label with dexfenfluramine or fenfluramine until they were withdrawn from the U.S. market in 1997 because of valvulopathy concerns). The 14 deaths (listed in APPENDIX II) are associated with suspected overdose (6 cases, [unclear if intentional or accidental]), drug interactions (patients with mental health disorders taking psychiatric drugs: 3 cases, rizatriptan: 1 case, and liothyronine: 1 case), and one case each associated with arrhythmia, stroke, and in utero exposure.

2.3 TOPIRAMATE (TOPAMAX)³

Topiramate, initially approved in 1996, is indicated for use in the management of epilepsy (recommended dose is 200-400 mg daily) and migraine headache prophylaxis (recommended dose is 100 mg daily). Topiramate has also been studied and used off label for weight loss.⁴ The mechanism of topiramate is unclear, but may center around sodium channel blockade, carbonic anhydrase (weak) inhibition, augmentation of GABA-A receptors, and antagonism of AMPA/kainate subtype of the glutamate receptor.

In regards to the safety profile, topiramate, like phentermine, has both 1) dose-related effects (cognitive impairment, hyperammonemia) and idiosyncratic reactions (glaucoma). Topiramate has no contraindications for use, but the labeling highlights a number of important drug-related adverse events (WARNINGS and PRECAUTIONS):

- Acute myopia and secondary angle closure (typically occurs within one month of initiating therapy; can lead to permanent vision loss if untreated)
- Oligohidrosis and hyperthermia (majority of reports involve pediatric patients)
- Suicidal behavior and ideation (class labeling for antiepileptic drugs)
- Metabolic acidosis (caused by renal bicarbonate loss due to topiramate's inhibitory effect on carbonic anhydrase; bicarbonate average decrease of 4 mEq/L at topiramate daily dose of 400 mg)
- Cognitive dysfunction, psychiatric/behavioral disturbances (depression or mood problems), and somnolence or fatigue
- Hyperammonemia and encephalopathy
- Kidney stones
- Paresthesia (common effect)

Topiramate may cause serious adverse fetal effects, based on pregnancy registry and nonclinical data. The pregnancy registry data suggest that there may be an association between the use of topiramate during pregnancy and congenital malformations (craniofacial defects such as cleft lip/palate, hypospadias, and anomalies involving various body systems).

Topiramate has a Medication Guide to prevent or increase awareness of serious side effects, including eye problems, decreased sweating and increased body temperature, and suicidal thoughts or actions.

AERS

Adverse events that are frequently reported to AERS (listed in APPENDIX III) and associated with topiramate when used for migraine headache prophylaxis* are consistent with the topiramate labeling. Of note in the top 25 reported adverse events the leading terms are eye disorders (glaucoma), paresthesia, and psychiatric disorders (confusion, depression) – events that are known to be associated with topiramate, but the mechanism is poorly understood.

Topiramate Deaths

AERS contains 10 reports of death associated with topiramate and migraine headache prophylaxis* that were received by FDA, marketing through December 31, 2009. The 10 reports of death (presented in APPENDIX IV) were poorly documented. Two cases did not report the cause of death, two cases were associated with psychiatric disorders (overdose and completed suicide), and there was one case each of floppy mitral valve syndrome, cardiovascular disease, ARDS, sudden death, in utero exposure, and spontaneous abortion.

* Reports limited to those associated with migraine headache prophylaxis because the Qnexa intended population will include patients without epilepsy, and secondly, the recommended topiramate dosage for migraine prophylaxis [25-100 mg daily] more closely approximates the proposed dosage for Qnexa [23-92 mg daily] than the dosage recommended for epilepsy [200-400 mg daily].

3 METHODS

3.1 AERS SEARCH STRATEGY

AERS was searched on April 6, 2010 using the search criteria in Table 3 below.

Table 3. Search Criteria for Used to Identify Phentermine and or Topiramate Cases in AERS	
<i>Product(s):</i>	Interaction Search Product 1: Topiramate (Topamax) Product 2: Phentermine (Adipex-P, Ionamin, Fastin) Products-Trade Name: Qnexa (separate search)
<i>Search Terms:</i>	All
<i>Search Dates:</i>	Marketing through 31Dec2009
<i>Countries:</i>	All (United States & foreign)
<i>Ages:</i>	All
<i>Combination Products:</i>	Yes
<i>Concomitant Products:</i>	Not dexfenfluramine or fenfluramine†
<i>Reason for Use:</i>	All
<i>Outcome:</i>	All (Serious and Nonserious)

*Cut off date chosen because dexfenfluramine and fenfluramine (both commonly coprescribed with phentermine) were withdrawn from the U.S. market in 1997

†The reports were downloaded and electronically limited to those reports that did not mention dexfenfluramine or fenfluramine in the ALLDRUGS field

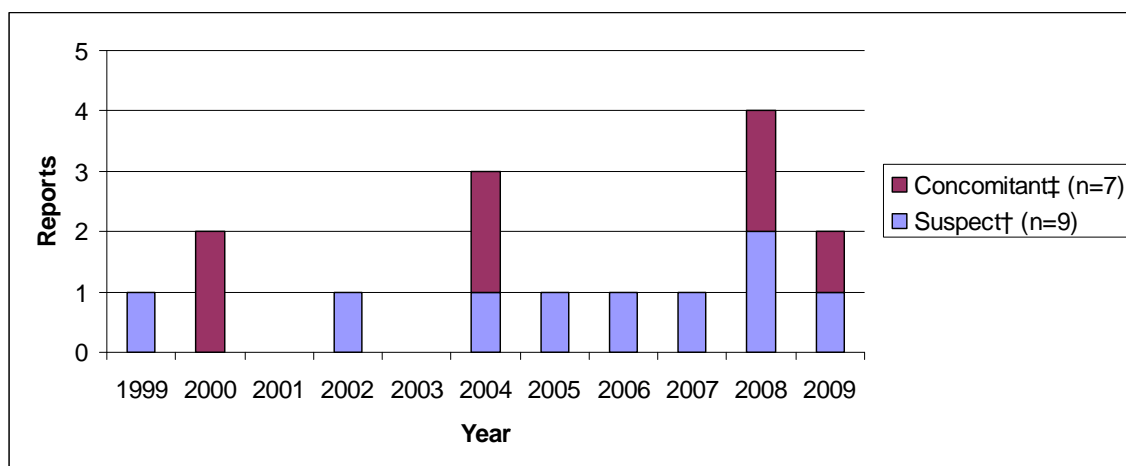
3.2 CASE SELECTION

We limited the AERS reports to spontaneous reports involving a patient on both topiramate and phentermine, but not fenfluramine or dexfenfluramine at the time of event (n=16). The search strategy in Section 3.1 identified 26 unique cases (all from the United States), of which we excluded 10 cases because they were not spontaneous reports (n=9), or the patient was not on phentermine and topiramate at the time of event (n=1). APPENDIX V lists the 10 excluded cases by ISR number.

4 RESULTS

Using the search criteria and case selection in Section 3 (Methods), AERS contains 16 cases (all from the United States) associated with concurrent use of topiramate and phentermine. Nine of the sixteen cases reported topiramate and or phentermine as suspect[†] drugs, and seven cases reported topiramate and phentermine as concomitant[‡] drugs. The 16 cases are presented by FDA receipt year in Figure 1.

Figure 1. Serious and Nonserious AERS Cases With Concurrent Use of Topiramate and Phentermine, by Reported Suspect Drug (n=9) or Concomitant Drugs (n=7) and FDA Receipt Year, Marketing through December 31, 2009



[†] Suspect drug: The reporter identified phentermine and or topiramate as “suspect” in causing the adverse event

[‡] Concomitant drug: The patient was taking phentermine and topiramate, but the reporter did not suspect them as causing the adverse event

Table 4 presents the characteristics of the 16 cases involving concurrent use of phentermine and topiramate. APPENDIX VI provides a brief description of each case.

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Phentermine and Topiramate (n=16). Source: AERS, Marketing Through Dec 31, 2009		
Characteristic		
Reporting Country		
	United States	16
Age (yrs)		
Median: 43	30-39 yrs	5
Range: 31-60	40-49 yrs	6
n=15	50-59 yrs	3
	60+ years	1
	Age not reported	1
Gender		
	Female	15
	Male	1
Weight (kg)		
Median: 62	< 100 kg	6
Range: 52-300	≥ 100 kg	3
n=9	Weight not reported	7
Phentermine Dose and Time To Event		
Dose reported		3
- daily dose (mg): 15, 37.5, 37.5		
Time to Event Reported		4
- therapy duration: 3 d, 10 d, 4 mo, 7 mo		
Topiramate Dose and Time to Event		
Dose Reported		8
- daily dose (mg) : 25 (1), 50 (3), 75 (2), 100 (2)		
Time to Event Reported		8
- therapy duration: <2 wks (4), ~1 mo (2), 3 mo (1), 3 yr (1)		

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Phentermine and Topiramate (n=16). Source: AERS, Marketing Through Dec 31, 2009		
Characteristic		
Reported Event by System Organ Class (# of cases) -Adverse Event (Reported Suspect Drug)	Topiramate/ Phentermine Reported as Suspect†	Topiramate/ Phentermine Reported as Concomitant‡
Eye Disorders (7 cases) -Blepharospasm (Abilify): 1 -Acute secondary glaucoma/Angle closure glaucoma/ Treated with “glaucoma” drug (topiramate): 3 -Acute loss of vision (topiramate): 1 -Blurred vision/Eye swelling NOS (topiramate): 2	6	1
Psychiatric Disorders (2 cases) -“Brain fog,” “Passed out,” “Fall” (topiramate): 1 -Psychosis, Delirium (topiramate, Paxil, phentermine): 1	2	--
Musculoskeletal Disorders (2 case) -Muscle cramps (Simcor, Crestor): 2	--	2
Gastrointestinal Disorders (1 case) -Ischemic colitis (phentermine): 1	1	--
Skin Disorders (1 case) -Pyoderma gangrenosum flare (Enbrel): 1	--	1
Nervous System Disorders (1 case) -Sleepiness with MVA (Effexor, clonazepam, Seroquel, Xanax): 1	--	1
Multiple System Organ Classes (2 cases) -Weakness, Tremors, Decreased concentration, Dyspnea, Hypotension, Nausea, Sweating, Incontinence, throat “felt swollen,” Dysphagia (Neurontin, Thorazine): 1 -Increased liver enzymes, Agitation, Nausea, Insomnia, “Crawling feeling” (Wellbutrin) : 1	--	2

†Suspect drug: The reporter identified phentermine and or topiramate as “suspect” in causing the adverse event

‡Concomitant drug: The patient was taking phentermine and topiramate, but the reporter did not suspect them as causing the adverse event

Table 4. Characteristics of AERS Cases (Serious and Nonserious) Associated With Concurrent Use of Phentermine and Topiramate (n=16). Source: AERS, Marketing Through Dec 31, 2009	
Characteristic	
Reported Medical History	
Psychiatric Medical History	8
- Bipolar disorder (2)	
- Bipolar disorder, schizophrenia (1)	
- Depression (2)	
- Depression with anxiety or panic disorder (2)	
- Drug abuse, HTN, sleep disorder (1)	
Other Medical History	6
- Hypothyroidism (1)	
- Hypothyroidism, HTN, headache (1)	
- Hypothyroidism, diabetes, Afib (1)	
- Dyslipidemia (1)	
- Migraines (1)	
- Pyoderma gangrenosum (1)	
Reported as “no relevant” medical hx	2
Reported Concomitant Medications* (all 16 cases reported medication history)	
Antidepressants (bupropion [Wellbutrin] 3, duloxetine [Cymbalta] 2, venlafaxine (Effexor) 2, fluoxetine [Prozac] 1, paroxetine [Paxil] 1)	9
Benzodiazepine	6
Antipsychotics	3
Opioids	3
Reporter Source	
Consumer	5
Healthcare provider	11

*Numbers may not sum because cases may report more than one concurrent medication

5 DISCUSSION

Given two-third of adults in the United States are either overweight or obese,⁵ weight loss products, such as Qnexa, may have widespread exposure, and the potential for associated safety issues must be considered.

This review identified important safety concerns for Qnexa (also described in the phentermine and topiramate labelings) that include congenital malformations, eye disorders, neuropsychiatric events, and cardiovascular events (including death). The intended population (obese or overweight) is susceptible to comorbidities such as cardiovascular death⁶ that may be exacerbated by the dose-related sympathomimetic effects of the phentermine component of Qnexa. Phentermine is contraindicated in patients with cardiovascular disease, but cardiovascular disease is often asymptomatic, which would complicate optimal patient selection with this agent.

The potential for serious Qnexa interactions can not be overlooked since this review identified reports (including death) that involved suspected drug interactions. For example (ISR 142294), a physician suspected a drug interaction between liothyronine (Cytomel) and phentermine in the death of a female (age not reported). Another physician (ISR 1535141) suspected a phentermine drug interaction in the death of a 42-year-old with no “cardiovascular disease” who was taking phentermine and dihydroergotamine, and died within 24 hours of taking sumatriptan. This review also suggests Qnexa may be used in patients with mental health disorders (and taking psychiatric drugs) who may be susceptible to phentermine’s CNS stimulant effects (inhibition of norepinephrine and dopamine reuptake). For example (ISR 4022031), a physician reported a 48-year-old female with a history of “stable depression and panic disorder” for five years (on paroxetine, topiramate and clonazepam) who was hospitalized with psychosis after starting phentermine that the patient had purchased on the Internet.

Lastly, the safety profile associated with long term use of Qnexa is not known. It is notable that phentermine was approved only for short term use (“a few weeks”) for patients with obesity. Topiramate was approved for long term use, but in a population (epilepsy or migraine prophylaxis) that may have important clinical differences than patients who seek treatment for obesity.

6 CONCLUSIONS AND RECOMMENDATIONS

Both phentermine and topiramate have been approved as single ingredient products in the United States for more than 10 years. However, little is known about the postmarket safety profile when phentermine and topiramate are used concurrently in an overweight or obese population. Given two-third of adults are either overweight or obese,⁵ Qnexa could have widespread use, and the potential for safety issues cannot be dismissed.

Approval of Qnexa should take into account the safety profile not only of the combination product, but the individual components as well. The safety issues that should be evaluated and considered include:

1. Cardiac Disorders (arrhythmias, changes in blood pressure, tachycardia, and ischemic heart disease)
2. General Disorders (drug interactions, including those with oral contraceptives, antipsychotics, SSRIs, other stimulant drugs, and weight loss products)
3. Metabolic and Nutrition Disorders (metabolic acidosis, oligohidrosis and hyperthermia)
4. Nervous System Disorders (cognitive impairment, somnolence, paresthesia)
5. Ophthalmic Disorders (glaucoma)
6. Pregnancy and Lactation (congenital anomalies, pediatric exposure during lactation)
7. Psychiatric Disorders (depression, suicide, anxiety, psychomotor changes, drug abuse, misuse, withdrawal, dependence)
8. Renal and Urinary Disorders (kidney stones)
9. Respiratory Disorders (primary pulmonary hypertension)
10. Safety associated with long term use

The sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) and a Phase 4 outcomes study. DPV defers to the Divisions of Epidemiology (DEPI) and Risk Management (DRISK) to assist in the review of such proposed REMS and postmarket studies.

¹ Celltech Pharmaceuticals. Ionamin (phentermine resin) prescribing information. Rochester NY. 2003 Mar.

² Food and Drug Administration. Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux) [Internet]. Silver Spring, MD. 2005 Jul 7. Available from:
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm>

³ Ortho-McNeil Neurologics, Ortho-McNeil-Janssen Pharmaceuticals. Topamax (topiramate) prescribing information. Titusville NJ. 2009 Dec. Available from:
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APPENDIX I. Phentermine: Reported Adverse Events

Table 1. Top 25 Adverse Events Reported with PHENTERMINE (Excludes Fenfluramine and Dexfenfluramine Reports), Organized by System Organ Class (SOC) and Preferred Term. Source: AERS, U.S. Serious Cases, Marketing Through 31Dec1996*

SOC	Preferred Terms (crude counts)	Total Counts for SOC
Cardiac Disorders		
	Hypertension (8), Arrhythmia (6), Tachycardia (5), Cardiac arrest (4)	23
Gastrointestinal Disorders		
	Abdominal pain (6)	6
General Disorders and Administration Site Disorders		
	Chest pain (6), Drug ineffective (6)	12
Injury, Poisoning, and Procedural Complications		
	Overdose (6), Accidental overdose (6), Drug interaction (5), Drug level above therapeutic (5), Drug withdrawal (4)	26
Metabolic and Endocrine Disorders		
	Hypokalemia (4)	4
Nervous System Disorders		
	Cerebrovascular accident (7), Convulsion (6), Amnesia (4)	17
Psychiatric Disorders		
	Depression (10), Psychotic disorder (8), Confusional state (5), Hallucination (5), Agitation (4), Schizophrenia (4), Schizophreniform disorder (4)	40
Respiratory, Thoracic and Mediastinal Disorders		
	Dyspnea (4)	4
Skin and Subcutaneous Disorders		
	Alopecia (4)	4

*AERS was searched on April 6, 2010 for phentermine reports (U.S. serious only) using the generic (phentermine) and brand names (Adipex, Ionamin, Fastin). The cut off date was December 31, 1996 , which was chosen because phentermine was coprescribed off label with dexfenfluramine and fenfluramine until they were withdrawn from the U.S. market in 1997 because of valvulopathy concerns. The reports were downloaded and limited to those without mention of dexfenfluramine or fenfluramine in the ALLDRUGS field.

APPENDIX II. Phentermine Deaths (n=14)

Appendix II. Phentermine Reports in AERS Associated with Death, Marketing Approval (1959) through December 31, 1996. Excludes Cases With Concurrent Use of Dexfenfluramine or Fenfluramine, n=14				
ISR # Rcv Yr	Age Sex	Concomitant Drugs	Comment	Description
135243 1982	42 y Female	tranylcypromine [Parnate], trifluoperazine (Stelazine), methylphenidate, phenylpropanolamine, ergotamine	Suspected drug interactions	42 yof with history of a mental health disorder (on tranylcypromine [Parnate], trifluoperazine (Stelazine), and methylphenidate [Ritalin]) died nine days after hospital discharge. After discharge the woman received phenylpropanolamine and phentermine from a "diet doctor." She presented in the ER with a "headache," was given ergotamine (Gynergen) and died that day.
707493 1990	34 y Female	Overdose (aspirin, alcohol, diazepam)	Overdose	34 yof died 16 hours after a drug overdose of alcohol, aspirin, phentermine, diazepam, and possibly propoxyphene and acetaminophen
760982 1991	--- Female	NA	Overdose	Female (age unknown) died following a suspected overdose with phentermine. However, the phentermine blood level was found "subtherapeutic" at 27 mcg/mL.
1795653 1996	37 y Male	Phendimetrazine	Cardiac death	Legal report of a 37 yom with history of recent onset of angina died of a cardiac arrhythmia two days after starting phentermine (30 mg) and phendimetrazine. Autopsy revealed cardiomegaly and "severe CAD."
451228 1987	--- ---	NA	In utero exposure	A woman took phentermine for 1-2 weeks during the first trimester of pregnancy. The child died during labor and was found to have "congenital heart disease" characterized by transposition of the great vessels, ventricular septal defect, and absent valve.
367024 1985 1986	32 y Male	Chlorpromazine, amobarbital, ethchlorvynol	Suspected drug interactions	Published report of a 32 yom with a history of drug abuse was found dead after taking two chlorpromazine tablets (dose unknown). The man was also taking amobarbital, ethchlorvynol, and phentermine.

Appendix II. Phentermine Reports in AERS Associated with Death, Marketing Approval (1959) through December 31, 1996. Excludes Cases With Concurrent Use of Dexfenfluramine or Fenfluramine, n=14

ISR # Rcv Yr	Age Sex	Concomitant Drugs	Comment	Description
1535141 1994	42 y Male	sumatriptan, dihydroergotamine	Suspected drug interaction	A 42 yom with history of migraines but no "cardiovascular disease" started sumatriptan (Imitrex). Six weeks later, and within 24 hours of a dose of sumatriptan, the man "died while sleeping." The man was also taking dihydroergotamine. Autopsy revealed the cause of death to be "stenosis of left main coronary artery."
1682676 1995	44 y Female	Unknown	Increased phentermine blood level	44 yof with history of seizures, died six months after starting phentermine. Her phentermine blood level was 180 mcg/mL 12 hours after her last phentermine dose.
142294 1982	--- Female	liothyronine	Suspected drug interaction	Female (age unknown) experienced "cardiac arrhythmia and death due to interaction between Cytomel [liothyronine] and phentermine." No additional information available
682777 1990	26 y Female	Unknown antibiotics	Suspected overdose	A 26 yof (weight 96 pounds) was found dead 24 hours after starting unspecified antibiotic therapy for pneumonia. Autopsy revealed "0.03 mg % Fastin blood level. ? Overdose. Cause of death: pneumonia."
592035 1989	34 y Male	trimipramine, lithium, alprazolam	Suspected drug interaction	34 yom with history of mental health disorder (on trimipramine, lithium, and alprazolam) died 12 days after starting phentermine 30 mg daily. The autopsy reports states the death "resulted from the acute combined toxicity of tricyclic trimipramine and the anorexiant catecholamine drug phentermine."
620436 1989	--- ---	NA	Overdose	Report of death (age and gender unknown) possibly due to phentermine overdose. The autopsy revealed "toxic" phentermine blood levels (0.76 mg/dL)
590956 1989	35 y Female	Unknown	Overdose	35 yof died of "probable heart damage as a result of taking four times the recommended dose."
1527729 1994	55 y Female	clonidine, HCTZ	Stroke	A 55 yof (on clonidine and HCTZ) died after experiencing a left occipital intracerebral hemorrhage and left subdural hematoma an unknown time after starting phentermine.

APPENDIX III. Topiramate: Reported Adverse Events

APPENDIX III. Top 25 Adverse Events Reported with TOPIRAMATE When Used for Migraine Headache Prophylaxis, Organized by System Organ Class (SOC) and Preferred Term. Source: AERS, U.S. Serious Cases, Marketing through 31Dec2009*		
SOC	Preferred Terms (crude counts)	
Eye Disorders		
	Angle closure glaucoma (86), Vision blurred (79), Myopia (52), Eye pain (51), Blindness (35), Glaucoma (35), Visual acuity reduced (34)	372
Gastrointestinal Disorders		
	Nausea (64)	64
General Disorders and Administration Site Disorders		
	Fatigue (47), Product Substitution Issue (45), Drug Ineffective (37)	129
Investigations		
	Weight Decreased (96)	96
Nervous System Disorders		
	Headache (92), Migraine (73), Paresthesia (68), Dizziness (58), Convulsion (36), Hypoaesthesia (35)	362
Psychiatric Disorders		
	Confusional State (53), Depression (45), Disturbance In Attention (39), Suicidal ideation (37)	174
Renal and Urinary Disorders		
	Nephrolithiasis (35)	35
Respiratory, Thoracic and Mediastinal Disorders		
	Dyspnea (38)	38
Skin and Subcutaneous Disorders		
	Alopecia (34)	34

*AERS was searched on April 6, 2010 for topiramate reports (U.S. serious only) using the generic (topiramate) and brand (Topamax) names. The cut off date was December 31, 2009. The reports were downloaded and limited to those mentioning migraine or headache in the IND fields. The reports limited to those associated with migraine headache prophylaxis because the Qnexa intended population will include patients without epilepsy, and secondly, the recommended topiramate dosage for migraine prophylaxis [25-100 mg daily] more closely approximates the proposed dosage for Qnexa [23-92 mg daily] than the dosage recommended for epilepsy [200-400 mg daily].

APPENDIX IV. Topiramate Deaths (n=10)

Appendix IV. Topiramate Reports in AERS Associated with Migraine Headache (Reason for Use) and an Outcome of Death, Marketing Approval (1996) Through December 31, 2009.				
ISR # Recv Yr	Age Gender	Concomitant Drugs	Comment	Description
3995916 2000	56 y Female	rizatriptan	Floppy mitral valve syndrome	A 56 yof with a history of migraines died in her sleep six weeks after starting topiramate. She started topiramate 25 mg daily, and the dose was titrated weekly to 100 mg BID. She complained of slurred speech, GI symptoms, and "fuzziness," and the dose was decreased to 100 mg at bedtime. She was also taking rizatriptan, but hadn't taken any for 2-3 days prior to her death. The autopsy reported indicated the cause of death was floppy mitral valve syndrome.
4212259 2003	25 y Female	oral contraceptive	Spontaneous abortion	A 25 yof (taking an oral contraceptive) experienced a spontaneous abortion while taking topiramate 150 mg daily for migraines
4471388 2004	47 y Male	fentanyl, rizatriptan, promethazine, and levetiracetam	Completed suicide	A 47 yom died of a self-inflicted gunshot wound six days after starting topiramate.
4861495 2005	--- Female	Unknown	---	A female (age unknown) died two days after receiving topiramate 25 mg samples from her physician for migraines. No additional information provided
5006641 2006	46 y Female	dicyclomine, clindamycin, rabeprazole, alprazolam, mesalamine, methadone, Dyazide, Vicodin, and chlorzoxazone	Atherosclerotic cardiovascular disease	A 46 yof (weight 148 lbs) was "found dead" an unknown time after starting topiramate 25 mg TID. Prior to her death, she complained of "stomach cramps and vomiting." The cause of death was atherosclerotic cardiovascular disease. She was taking multiple medications

Appendix IV. Topiramate Reports in AERS Associated with Migraine Headache (Reason for Use) and an Outcome of Death, Marketing Approval (1996) Through December 31, 2009.

5088926 2006	41 y Female	hydromorphone, Vicodin, bupropion, prednisone and duloxetine	Overdose	A 41 yof died following a multiple drug overdose while taking topiramate 300 mg daily for migraines.
5072459 2006	--- Male	Unknown	---	A male (age unknown) died while taking topiramate 200 mg daily for migraine prevention. No additional information provided
5230352 2007	34 y Female	Unknown	ARDS	A 34 yof with a history of schizophrenia died of acute respiratory distress syndrome approximately a year after starting topiramate for migraine prophylaxis. The patient had been taking 200 mg daily, but the dose was increased to 300 mg daily a month before her death.
5350961 2007	--- Female	Unknown	Sudden death	A female (age unknown) died "unexpectedly" a few days after receiving a topiramate starter pack (#42, 25 mg tablets) for migraine prevention. No additional information available.
6075807 2009	1 d Male	---	In utero exposure	A neonate died at 19 hours of age due to a porencephalic cyst. While in utero, he was found to have fetal lateral ventricles enlarged, fetal large midline intracranial mass, fetal cerebral cortex thinned and fetal left frontal hydrocephalus. He was exposed (transplacental) throughout the pregnancy to topiramate 300 mg daily (for migraine), gabapentin, and quetiapine for sleep disorder, and buprenorphine for 7 months.

APPENDIX V. Excluded Cases (n=10)

ISR No. RCV Year Reporter	Age Gender WT	Reported Suspect Drug	Reported Event	Reason for Exclusion
4480059 2003 Legal	47 yr Fe 118 kg	Ziprasidone (Geodon), Erythromycin, Rofecoxib (Vioxx), Oxycodone/APAP	Stroke	Attorney report
4684354 2004 Legal	48 yr Fe 68 kg	Fluoxetine (Prozac), Olanzapine (Zyprexa)	Suicide attempt, Behavior changes	Attorney report
4665628 2005 Legal	39 yr Fe 128 kg	Olanzapine (Zyprexa)	Suicide ideation, Increased appetite, Leg edema, Numbness	Attorney report
4791047 2005 AAPCC*	33 yr M ---	Diphenhydramine (Benadryl) Propoxyphene (Darvon), Phentermine, Citalopram (Celexa), APAP (Tylenol)	Completed Suicide (polydrug intoxication)	Surveillance report (annual poison control publication)
5330794 2007 MD	35 yr M ---	Zonisamide (Zonegran)	Vanishing bile duct syndrome	Not on topiramate at time of event
6370900 2007 Legal	32 yr M 170 kg	Quetiapine (Seroquel)	Diabetes, Pancreatitis	Attorney report
6370880 2007 Legal	27 yr Fe 71 kg	Quetiapine (Seroquel)	Hyperglycemia, Pancreatitis	Attorney report
6370039 2007 Legal	31 yr Fe 91 kg	Quetiapine (Seroquel), Aripiprazole (Abilify), Olanzapine (Zyprexa), Risperidone (Risperdal), Ziprasidone (Geodon)	Diabetes	Attorney report
5278432 2007 Consumer	51 yr Fe 107 kg	Peg-Intron, Ribavirin	Dehydration	Hepatitis C postmarket surveillance program (Be in Charge)
6609963 2010 Legal	58 yr Fe 90 kg	Fentanyl, Topiramate	Multiple drug intoxication	Attorney

APPENDIX VI. Concurrent Use Cases (n=16)

Appendix VI. AERS Cases Associated with Concurrent Use of Phentermine and Topiramate, Marketing through December 31, 2009 (n=16)				
ISRNUM	AGE	Medical History (Concomitant Meds)	Reported Suspect Med	Case Description
3358180 1999 US	43y Fe ---	Bipolar disorder (mirtazapine, venlafaxine, gabapentin, benzo)	topiramate	Consumer reports 43 yof experienced dizziness, headache and periorbital edema (" could not open her eyes ") 1 week after starting topiramate (on phentermine unknown duration). Topiramate discontinued (phentermine continued), and swelling decreased.
3476700 2000 US	31y Fe 52 kg	Bipolar disorder, schizophrenia (gabapentin, chlorpromazine, fluoxetine, buspirone, COX2I, risperidone, quetiapine, benzos)	gabapentin, chlorpromazine	Consumer reports 31 yof experienced muscle weakness, tremors, decreased concentration, dyspnea, hypotension, nausea, sweating, incontinence, throat "felt swollen," and dysphagia less than one month after starting topiramate (on phentermine 4 months). SSEP normal. Gabapentin and chlorpromazine discontinued. Pt has not recovered.
3580676 2000 US	44y Fe ---	Depression, Anxiety, Sleep apnea, Anemia, Fibromyalgia (venlafaxine, quetiapine, phendimetrazine, benzos)	venlafaxine, quetiapine, benzos	Consumer reports 44 yof experienced sleepiness and associated MVA an unknown time after starting topiramate (on phentermine 7 months and venlafaxine 3-5 months). Follow up indicates the patient remains on all the "same dosages" and is "doing great."
4022031 2002 US	48y Fe 300 kg	Depression, Panic Disorder (paroxetine)	phentermine, topiramate, paroxetine	Physician reports a 48 yof with a history of "stable depression and panic disorder" on paroxetine, topiramate and clonazepam for five years. An unknown time after starting phentermine (purchased on the Internet) the patient experienced psychosis (delirium). The patient recovered and is now taking topiramate, ziprasidone, and venlafaxine

Appendix VI. AERS Cases Associated with Concurrent Use of Phentermine and Topiramate, Marketing through December 31, 2009 (n=16)				
ISRNUM	AGE	Medical History (Concomitant Meds)	Reported Suspect Med	Case Description
4373519 2004 US	58 y Fe 81 kg	Diabetes, Afib, Hypothyroidism (rosuvastatin, PPI, levothyroxine, allopurinol, metformin, HCTZ, warfarin)	rosuvastatin	Consumer reports a 58 yof experienced muscle tightness and cramps six days after starting rosuvastatin (on topiramate and phentermine unknown duration)
4508142 2004 US	61y Fe 110 kg	Depression (bupropion)	bupropion	Physician reports a 61 yof experienced increased " liver enzymes " (ALT 238, AST 82) agitation, nausea, insomnia, and "crawling feeling" one month after starting bupropion (on topiramate and phentermine unknown duration)
4511360 2004 US	43y Fe 84 kg	"None significant" (PPI)	phentermine	Physician reports a 43 yof experienced bloody diarrhea (diagnostic testing consistent with ischemic colitis) 3 days after starting phentermine and topiramate. Outcome unknown
4908282 2005 US	39 y Fe 82 kg	Hypothyroidism (levothyroxine)	topiramate	Physician reports 39 yof experienced angle closure glaucoma 10 days after starting topiramate and phentermine. Topiramate and phentermine discontinued; treated in the emergency room. Patient recovered
5149891 2006 US	35 y Fe ---	"None significant" (none)	topiramate	Physician reports 35 yof experienced acute secondary glaucoma with vision loss one week after starting topiramate and phentermine. Topiramate was discontinued and the intraocular pressure "decreased to almost normal within a day or two."
5474907 2007 US	--- Fe ---	Migraine (bupropion)	topiramate	Physician reports female (age unknown) "woke up with complete vision loss " one week after starting topiramate. Patient appeared to "have uveal effusions." Topiramate was discontinued. Outcome not provided.

Appendix VI. AERS Cases Associated with Concurrent Use of Phentermine and Topiramate, Marketing through December 31, 2009 (n=16)				
ISRNUM	AGE	Medical History (Concomitant Meds)	Reported Suspect Med	Case Description
5865390 2008 US	32y Fe ---	Dyslipidemia (niacin, simvastatin, duloxetine, benzo)	niacin/simvastatin	Consumer reports a 32 yof experienced muscle cramps two days after starting niacin/simvastatin (Simcor). The patient was also taking phentermine and topiramate (duration unknown). Simcor was not discontinued; the muscle cramps were ongoing
5998646 2008 US	49y Fe ---	Pyoderma gangrenosum (duloxetine, PPI, estrogen, gabapentin, opioid, COX2I, trazodone, warfarin)	Enbrel (DC 6 mo before event)	Physician reports a 49 yof experienced a flare of pyoderma gangrenosum (previously treated with Enbrel) an unknown time after starting phentermine and topiramate
6040252 2009 US	53 y Fe ---	Bipolar disorder (levothyroxine, metformin, aripiprazole, miglitol, benzo)	aripiprazole	Physician reports a 53 yof experienced a blepharospasm with "severe or permanent disability" while on numerous medications (phentermine and topiramate unknown duration). The reported assessed that the blepharospasm was possibly related to tapering of the aripiprazole.
5759903 2008 US	37y Fe 104 kg	HTN, hypothyroidism, headaches ("thyroid," lisinopril)	topiramate	Nurse practitioner reports a 37 yof experienced eye symptoms (pain, swelling, blurriness) one day after taking four of her mother's 25 mg topiramate tablets for two days. The pt had been taking 100 mg topiramate daily for three weeks, but ran out of her prescribed 100 mg tablets. She was treated with "glaucoma drops," recovered, and continues taking the 100 mg tablets. Cross reference with case ISR 6221574 (mother)

Appendix VI. AERS Cases Associated with Concurrent Use of Phentermine and Topiramate, Marketing through December 31, 2009 (n=16)				
ISRNUM	AGE	Medical History (Concomitant Meds)	Reported Suspect Med	Case Description
6221574 2008 US	56y Fe 73 kg	Depression, headaches (bupropion, estrogen)	topiramate	Nurse practitioner reports a 56 yof experienced eye symptoms (twitching and pressure "like a headband") a "short period of time" after starting phentermine and topiramate 25 mg daily. The patient recovered, and the topiramate dose was increased to 75 mg daily. Cross reference case with ISR 5759903 (daughter)
6294772 2009 US	42 y M ---	Drug abuse, HTN, sleep disorder (NSAID, opioid, atenolol, benzo)	topiramate	Pharmacist reports a 42 yom " passed out " and experienced confusion ("feeling weird and forgetful," "brain fog") three months after starting topiramate (on phentermine unknown duration). Topiramate and phentermine discontinued.

NEUROLOGY

Topiramate in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register

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Topiramate in pregnancy

Preliminary experience from the UK Epilepsy and Pregnancy Register

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ABSTRACT

Objectives: Topiramate (Topamax®) is licensed to be used, either in monotherapy or as adjunctive treatment, for generalized tonic clonic seizures or partial seizures with or without secondary generalization and for prevention of migraine. The safety of topiramate in human pregnancy is largely unknown. Here we report on our experience of pregnancies exposed to topiramate.

Methods: This study is part of a prospective, observational, registration and follow-up study. Suitable cases are women with epilepsy who become pregnant while taking topiramate either singly or along with other antiepileptic drugs (AEDs), and who are referred before outcome of the pregnancy is known. The main outcome measure is the major congenital malformation (MCM) rate. Secondary outcomes include risk of specific MCM, minor malformation rate, birthweight, and gestational age at delivery.

Results: Full outcome data are available on 203 pregnancies. Of these, 178 resulted in live birth; 16 had an MCM (9.0%; 95% CI 5.6% to 14.1%). Three MCMs were observed in 70 monotherapy exposures (4.8%; 95% CI 1.7% to 13.3%) and 13 in cases exposed to topiramate as part of a polytherapy regimen (11.2%; 95% CI 6.7% to 18.2%). Four of the MCMs were oral clefts (2.2%; 95% CI 0.9% to 5.6%). Four cases of hypospadias were reported (5.1%; 95% CI 0.2% to 10.1%) among 78 known live male births of which two were classified as major malformations.

Conclusions: The number of outcomes of human pregnancies exposed to topiramate is low, but the major congenital malformation rate for topiramate polytherapy raises some concerns. Overall, the rate of oral clefts observed was 11 times the background rate. Although the present data provide new information, they should be interpreted with caution due to the sample size and wide confidence intervals. *Neurology*® 2008;71:272-276

GLOSSARY

AED = antiepileptic drug; MCM = major congenital malformation; SGA = small for gestational age.

It is widely accepted that prenatal exposure to antiepileptic drugs (AEDs) increases the risk of major congenital malformations (MCM) from the background risk of 1% to 2%¹⁻³ to between 4% and 9%.³⁻⁵ However, except for lamotrigine,^{5,6} levetiracetam,⁷ and oxcarbazepine,⁸ information is limited on the other newly available AEDs (vigabatrin, gabapentin, topiramate, tiagabine, pregabalin, and zonisamide).

Topiramate is licensed for use both in monotherapy and as adjunctive treatment for generalized tonic clonic seizures or partial seizures with or without secondary generalization. During 2004 it was also licensed by the Food and Drug Administration for prophylaxis of migraine.

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Table 1 Outcomes of pregnancies exposed to topiramate		
	Topiramate monotherapy exposures	Topiramate as part of a polytherapy regimen
No. of exposures	70	133
Outcome		
Live births	62	116
Spontaneous abortions	6	12
Induced abortions	2	3
Stillbirths	0	2
Mean dose TPM (range), mg	245 (50-800)	299 (25-1,000)
Mean gestational age at enrollment (range), wk	14.5 (4-34)	14.9 (4-34)
Mean gestational age at delivery, wk	39.2	38.8
Mean birthweight, g	3,168	3,062
Sex		
Male	25	53
Female	35	61
Not recorded	10	19
Mode of delivery		
Spontaneous vaginal deliveries	35	59
Cesarean	17	34
Forceps	5	11
Ventouse	4	6
Abortions	7 (2 induced)	15 (3 induced)
Not recorded	2	8
Seizures in pregnancy		
Tonic-clonic ± other	15	45
Minor only	14	27
None	31	33
Not recorded	10	28
Major malformations [rate (95% CI)]	3 [4.8% (1.7-13.3%)]	13 [11.2% (6.7-18.2%)]
Any malformation [rate (95% CI)]	7 [12.9% (6.7-23.4%)]	23 [19.8% (13.6-28.0%)]

TPM = topiramate.

Topiramate has been shown to be teratogenic in mice, rats, and rabbits.⁹ In mice doses as low as 0.2 times the maximum recommended human dose (400 mg/m²) were asso-

ciated with an increased frequency of (primarily) craniofacial defects.

Safety data for topiramate in human pregnancy are limited. A company sponsored abstract reported outcomes for 75 pregnancies exposed to topiramate.¹⁰ Of 29 monotherapy exposures two malformations (micrognathia, phimosis) were noted. Of the remaining 46 pregnancies that had also been exposed to at least one other AED seven infants had a malformation (cleft palate, cleft lip, tetralogy of Fallot, hand malformation, ureteral stenosis, pyloric stenosis, and one infant with cleft lip and palate, fixed extension of upper limb, bilateral radial deviation of hands, brachydactyly, and hydrocephalus).

METHODS The UK Epilepsy and Pregnancy Register is a prospective pregnancy register set up to determine the relative safety of all AEDs taken in pregnancy. Here we report our results for first-trimester exposures to topiramate, through August 31, 2007.

Suitable cases are women with epilepsy who became pregnant while taking topiramate, either singly or along with other AEDs, and who were referred before the outcome of the pregnancy was known. The main outcome measure was the MCM rate. Cases where any prenatal test (fetal ultrasound, blood test) had shown an abnormality and cases resulting in a pregnancy loss (induced abortion, spontaneous abortion, stillbirth) in which an abnormality had been identified before referral to the register had been made were excluded.

A major seizure is defined as a tonic-clonic seizure. A minor or other seizure denotes seizures without convulsive activity.

Outcome data were collected at 3 months after the expected date of delivery by sending the patient's general practitioner a standardized questionnaire for completion.

An MCM was defined as an abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered during the first 6 weeks of life. Disorders not conforming to this definition were assigned as minor malformations based on the definitions and lists of disorders in the EUROCAT registry.¹¹

The MCM rate was calculated as [total number of live births with an MCM] ÷ [total number of pregnancy losses with an MCM] ÷ [total number of live births] ÷ [total number of preg-

Table 2 Major congenital malformations with topiramate monotherapy									
No.	Dose TPM during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Major congenital malformation
1	200	29	G3P2	Partial	NR	41	3,850	F	Cleft lip and bilateral cleft palate
2	400	34	G3P2	NR	No	37	2,355	M	Hypospadias
3	600	27	G1P1	NR	Yes	39	3,289	NR	Cleft lip and palate

TPM = topiramate; GTC = generalized tonic-clonic seizure; NR = not recorded.

Table 3 Minor congenital malformations with topiramate monotherapy

No.	Dose TPM during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Minor congenital malformation
1	50	26	G5P4	GTC	No	37	2,200	F	Sacral dimple
2	750	30	G1P0	Partial	No	41	2,810	F	Clicky hips
3	300	32	G3P2	GTC	No	40	2,860	F	Plagiocephaly
4	100	23	NR	Partial	Yes	38	2,860	M	Toe webbing
5	200	25	G1P1	Partial	No	41	3,660	M	Immature hip joints

TPM = topiramate; GTC = generalized tonic-clonic seizure; NR = not recorded.

nancy losses with an MCM]. Spontaneous pregnancy losses and induced abortions where no abnormalities were reported were not included for analysis as we do not know if they were examined in detail and therefore cannot know the outcome. The total numbers presented for each group are therefore either the total number of outcomes or the total number of informative outcomes—that is, excluding pregnancy losses with no abnormalities reported. Full details on study methodology have been previously reported.⁵

RESULTS Through August 31, 2007, complete outcome data were available on 203 prospectively reported pregnancies that had had first trimester exposure to topiramate, of which 70 had been exposed to topiramate in monotherapy.

Pregnancy outcome details for all exposures are shown in table 1. Of all pregnancies exposed to topira-

mate, 178 (87.7%) resulted in a live birth. Of these, 31 pregnancies had an abnormality of some kind (17.4%; 95% CI 12.5% to 23.7%) with 16 of these being an MCM (9.0%; 95% CI 5.6% to 14.1%). Four MCMs were oral clefts (2.2%; 95% CI 0.9% to 5.6%) with three infants having both cleft lip and cleft palate. Four cases of hypospadias were reported (5.1%; 95% CI 0.2% to 10.1%) among 78 known live male births of which two were classified as major malformations. Full details on major and minor malformations are shown in tables 2 through 5.

For the three infants who had an MCM and who were exposed to topiramate in monotherapy the average total daily dose was 400 mg of topiramate compared to 238 mg in those without an MCM ($p =$

Table 4 Major congenital malformations with topiramate polytherapy

No.	Dose TPM during pregnancy/d, mg	Other AED doses during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Major congenital malformation
1	800	Clobazam 20; lamotrigine 550; vigabatrin 1,000	29	G2P1	Partial	No	40	2,381	M	Left hydronephrosis, dysmorphic
2	75	Ethosuximide 1,000; sodium valproate 1,000	39	G3P2	Partial	No	38	3,160	M	Pyloric stenosis
3	250	Lamotrigine 200	19	NR	NR	NR	NR	NR	F	Hernia and hydrocele
4	175	Lamotrigine 125	24	NR	Partial	No	38	2,530	F	Anal atresia
5	150	Sodium valproate 1,500	32	G2P1	GTC	Yes	42	3,660	M	Pyloric stenosis
6	150	Sodium valproate 200	24	G4P3	GTC	No	34	NR	F	Tracheoesophageal fistula
7	50	Sodium valproate 2,500	26	G3P2	GTC	Yes	41	3,400	M	Hypospadias
8	500	Sodium valproate 500	24	G1P0	NR	NR	40	2,455	F	Cleft palate, crossed toes
9	400	Lamotrigine 400	24	G1P0	GTC	NR	40	3,280	F	Bilateral dislocated hips
10	350	Lamotrigine 50	27	G2P1	JME	No	40	2,960	M	Harold type II Talipes, plagiocephaly
11	500	Carbamazepine 1,200; clobazam 10	28	G1P0	NR	Yes	38	NR	M	Congenital dislocated hip
12	800	Levetiracetam 500; lamotrigine 800	21	G1P0	Partial	Yes	33	2,460	M	Pyloric stenosis
13	250	Lamotrigine 300; phenobarbitone 60	37	G3P2	GTC	No	40	3,560	M	Left cleft lip and palate

TPM = topiramate; AED = antiepileptic drug; GTC = generalized tonic-clonic seizure; NR = not recorded; JME = juvenile myoclonic epilepsy.

Table 5 Minor congenital malformations with topiramate polytherapy

No.	Dose TPM during pregnancy/d, mg	Other AED doses during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Minor congenital malformation
1	100	Clobazam 20; lamotrigine 300; sodium valproate 1,000	30	G2P1	Partial	NR	37	2,920	M	Glandular hypospadias
2	800	Clobazam 10; lamotrigine 550; vigabatrin 1,000	27	G1P0	Partial	Yes	40	2,360	M	Abnormality of foreskin
3	400	Lamotrigine 600	21	G1P0	GTC	Yes	42	3,960	F	Dysmorphic features
4	100	Phenytoin 375; vigabatrin 2,000	25	NR	Partial	No	41	NR	F	Left ureteric reflux
5	300	Sodium valproate 1,500	21	G1P0	GTC	Yes	38	3,543	F	Patent ductus arteriosus
6	400	Carbamazepine 1,000; sodium valproate dose NR	18	G1P0	Partial	Yes	41	NR	M	Benign heart defect
7	50	Carbamazepine 800; sodium valproate 2,500	33	G1P0	GTC	Yes	39	3,230	F	Mild hypospadias
8	150	Carbamazepine 1,000	42	G1P0	Partial	No	38	3,535	F	Cavernous hemangioma
9	100	Carbamazepine retard 1,400; clobazam 10; levetiracetam 2,500	19	G1P0	Partial	Yes	40	3,210	F	Clicky right hip
10	150	Lamotrigine 200	36	NR	Primary generalized	No	41	3,850	F	Intra-abdominal cyst

TPM = topiramate; AED = antiepileptic drug; GTC = generalized tonic-clonic seizure; NR = not recorded.

0.123). Of the 61 cases exposed to topiramate in monotherapy for which there was information about gestational age, six infants (9.8%) were born at 37 weeks gestation or less. The average total daily dose for those born prematurely (250 mg) was not significantly different from those born after 37 weeks (246 mg ($p = 0.934$)). Of the 56 monotherapy outcomes for which there were full data on gestational age and birthweight, 8 (14.3%) were small for gestational age (SGA). The mean total daily dose for those who were SGA (346 mg) was not significantly different from those who were not SGA (239 mg, $p = 0.084$).

For polytherapy outcomes 32 combinations of at least one AED in addition to topiramate were recorded. Thirteen infants born with a major malformation were exposed on average to 342 mg per day of topiramate compared with 294 mg per day for live births without an MCM ($p = 0.539$). Of the 111 cases exposed to topiramate as part of a polytherapy regimen, for which there was information on gestational age, 17 infants (15.3%) were born at 37 weeks or less gestation. The mean total daily dose for those born prematurely (347 mg) was not significantly different from those born after 37 weeks (288 mg, $p = 0.891$). Of 103 live births exposed to topiramate as part of a polytherapy regimen and for which there were data regarding birthweight and gestational age, 20 infants (19.4%) were SGA. The mean total daily dose for those infants who were SGA (405 mg) was significantly different from those who were not SGA

(260 mg, $p = 0.019$). We have no data on maternal weights in pregnancy.

Co-administration of valproate with topiramate either as part of a duotherapy regimen ($n = 12$, MCM rate 36.4%; 95% CI 15.2 to 64.6%) or as part of a regimen of three or more AEDs ($n = 23$, MCM rate 23.8%; 95% CI 10.6 to 45.1%) was associated with the highest rates of MCM. This compared with a lower rate of MCM for exposures not including valproate ($n = 110$, MCM rate 8.4%; 95% CI 4.3% to 15.8%).

DISCUSSION The MCM rate for monotherapy exposures to topiramate was well within the range quoted for other AEDs.⁵ For polytherapy exposures the MCM rate was higher, consistent with previous reports comparing monotherapy and polytherapy exposures to all AEDs.³⁻⁵ The MCM rates for combinations containing valproate in addition to topiramate were higher than for combinations not containing valproate. While it is not clear if this is a consequence of an interaction between these drugs, is a reflection of unidentified patient characteristics, or is due to valproate, which has increasingly been shown to be associated with a high risk of MCMs, either in monotherapy or as part of a polytherapy regimen,^{5,12} is unclear. Clearly these results need to be replicated in larger numbers and from different registers before we might counsel women of child-bearing age

against using combinations including topiramate and valproate.

All of the MCMs observed have already been described in pregnancies exposed to AEDs other than topiramate and no apparent dose response was evident either for monotherapy or polytherapy exposures. We found the rates of oral clefts (2.2%) and hypospadias (5.1%) much higher than that reported in the United Kingdom. For oral clefts, which occur in 1 in 500 live births in the United Kingdom,¹³ the observed rate was 11 times higher than the background rate. For hypospadias, which is estimated to occur in 1 in 300 live births,¹⁴ the observed rate was approximately 14 times the background rate.

The mean birthweights for live infants exposed in utero to topiramate either as monotherapy or as part of combination therapy were within the normal range with a trend to lower birth weight in polytherapy exposures. Infants who were SGA were exposed to a significantly higher daily dose of topiramate but only when exposed to topiramate as part of combination therapy. In animal studies embryotoxicity (including reduced fetal weight gain) was observed at doses as low as 0.5 times the maximum recommended human dose.⁹ Unfortunately we have no data on maternal weights, either before or during pregnancy, and therefore cannot comment on any potential interaction between maternal weights and the outcome of SGA.

While our results are preliminary, they are relevant not only in dealing with women with epilepsy of childbearing years. Topiramate is also licensed for use for migraine prophylaxis, an even more common condition which also occurs frequently in women of childbearing years. While the risks for adverse outcomes, including teratogenic endpoints, may differ between patient groups exposed to the same drug but used for different indications, the teratogenic potential of any agent is also likely determined by factors related to the structure and functional effects of the agent, the dose prescribed, and the timing of use. This is also likely to be the case for topiramate. Monitoring pregnancies in women with migraine exposed to topiramate should therefore be encouraged.

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Topiramate in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register

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Guidance for Industry Developing Products for Weight Management

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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**U.S. Department of Health and Human Services
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**February 2007
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Revision 1

Guidance for Industry Developing Products for Weight Management

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Revision 1

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Guidance for Industry¹

Developing Products for Weight Management

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to industry regarding the development of drugs and therapeutic biologics (hereafter *products*) regulated within the Center for Drug Evaluation and Research (CDER) in the Food and Drug Administration (FDA) for the indication of weight management. This guidance applies to products intended to be used for medical weight loss, which can be defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipids, and HbA1c. This guidance revises the draft *Guidance for the Clinical Evaluation of Weight-Control Drugs* that issued in September 1996. When finalized, this guidance will replace the September 1996 draft guidance.

The September 1996 draft guidance is being revised to provide advice on conducting studies to evaluate the efficacy and safety of products for weight management in patients with medication-induced weight gain and weight management in obese pediatric patients. Recommendations on the design of studies evaluating the efficacy and safety of combinations of weight-management products are also provided.

This guidance does not explicitly discuss indications for weight loss or maintenance of lost weight (which also can be described as prevention of weight regain); however, weight loss and weight maintenance should be demonstrated over the course of at least 1 year before a product can be considered effective for weight management. Thus, the weight management indication incorporates and signifies weight loss and weight maintenance.

¹ This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

Contains Nonbinding Recommendations

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This guidance also does not discuss the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.²

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In January 2004, the FDA issued a notice in the *Federal Register* requesting public comment on the September 1996 draft guidance for the purpose of incorporating the latest scientific and clinical advances in weight management drug development. In September 2004, the FDA convened an advisory committee meeting to discuss the public comments received and to identify specific scientific, clinical, and regulatory issues that should be included in an updated guidance.

As a result, this revised guidance discusses several key areas of interest that are not covered in the September 1996 draft guidance. These areas include recommendations on the development of products for weight management in pediatric patients and in patients with medication-induced weight gain, and recommendations on the development of combinations of weight-management products.

III. OVERWEIGHT AND OBESITY CLINICAL BACKGROUND

A. The Adult Population

Obesity is a chronic, relapsing health risk defined by excess body fat. The pathogenesis of obesity involves the interaction of genetic, environmental, and behavioral factors. Total body fat can be accurately measured using hydrodensitometry and dual-energy x-ray absorptiometry (DEXA). Because body mass index (BMI), expressed as kilograms of weight divided by height in meters squared (kg/m^2), is simple and inexpensive to calculate, and correlates strongly with total body fat in non-elderly adults, it is commonly used as a surrogate for total body fat.

Excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers (Caterson and Hubbard et al. 2004; Calle and Thun et al. 1999). The relationships between BMI and risks for death and major comorbidities vary by age, sex, race, and smoking status, but, in general, are lowest in individuals with BMIs of $18.5 \text{ kg}/\text{m}^2$ to $24.9 \text{ kg}/\text{m}^2$ and increase in a curvilinear or linear manner with BMIs of $25 \text{ kg}/\text{m}^2$ to approximately $40 \text{ kg}/\text{m}^2$.

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Based on data relating BMI to mortality risk, the World Health Organization in 1995 and the National Institutes of Health in 1998 adopted the weight classifications by BMI that are shown in Table 1 (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998).

Table 1. Weight Classification Guidelines

Classification	BMI
Underweight	$< 18.5 \text{ kg/m}^2$
Normal weight	$18.5 \text{ kg/m}^2 - 24.9 \text{ kg/m}^2$
Overweight	$25 \text{ kg/m}^2 - 29.9 \text{ kg/m}^2$
Obesity (class 1)	$30 \text{ kg/m}^2 - 34.9 \text{ kg/m}^2$
Obesity (class 2)	$35 \text{ kg/m}^2 - 39.9 \text{ kg/m}^2$
Extreme obesity (class 3)	$\geq 40 \text{ kg/m}^2$

An increased level of visceral or intra-abdominal adiposity, independent of BMI, increases the risk for metabolic derangements and perhaps cardiovascular disease (Janssen and Katzmarzyk et al. 2004; Rexrode and Carey et al. 1998; Zhu and Wang et al. 2002). Visceral fat content can be accurately measured with computed tomography (CT) or magnetic resonance imaging (MRI). Waist circumference, like BMI, is inexpensive and easy to measure and correlates with CT- and MRI-derived measurements of visceral fat content (Pi-Sunyer 2004). In general, a waist circumference greater than 40 inches (greater than 102 cm) in men and greater than 35 inches (greater than 88 cm) in women is accepted as indicating increased visceral adiposity (The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 2000).

In overweight and obese individuals, particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss greater than or equal to 5 percent following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis and Macie et al. 2005).

Although some, but not all, observational studies suggest that modest degrees of intentional weight loss in overweight and obese individuals can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality, at the time of this writing, there are no data from randomized, controlled trials on the effects of drug-induced weight loss on these clinical outcomes (Parker and Folsom 2003; Eilat-Adar and Eldar et al. 2004; Gregg and Gerzoff et al. 2003).

Lifestyle modification, consisting of changes in patterns of dietary intake, exercise, and other behaviors, is considered the cornerstone of overweight and obesity management. Because all drug and biological therapies impose some risk for adverse events, the use of a weight-management product should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the anticipated benefits of weight loss are expected to outweigh the known and unknown risks of treatment with a particular weight-management product.

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Patients with BMIs greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² if accompanied by weight-related comorbidities historically have been considered appropriate populations for treatment with weight-management medications (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998). Although these patient-selection criteria are to a degree arbitrary, and an argument may be made for criteria that are more or less restrictive, we believe that individuals with BMIs greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² if accompanied by weight-related comorbidities represent patient groups with sufficient baseline risk to justify inclusion in studies of investigational weight-management products.

B. The Pediatric Population

As in adults, BMI correlates with more direct measures of adiposity in children and adolescents (American Academy of Pediatrics 2003; Barlow and Dietz 1998; Dietz and Robinson 2005; Speiser and Rudolf et al. 2005). Also similar to adults, BMI correlates with obesity-related comorbidities such as hypertension, dyslipidemia, and type 2 diabetes mellitus in pediatric patients.

In contrast to adults, the terms overweight and obese are used synonymously in pediatric patients (American Academy of Pediatrics 2003). The American Academy of Pediatrics (AAP) defines a pediatric-aged patient with an age- and sex-matched BMI of greater than or equal to 95th percentile as overweight or obese.

For patients aged 2 to 7 years, the AAP recommends weight loss through lifestyle modification if the BMI is greater than or equal to the 95th percentile for age and sex with the presence of one or more comorbidities. For patients who are 7 years of age or older, weight loss through lifestyle modification is recommended if the BMI is between the 85th and 95th percentile for age and sex with the presence of one or more comorbidities or if the BMI is greater than or equal to the 95th percentile for age and sex regardless of the presence of comorbidities.

Before therapeutic intervention, pediatric patients should receive a medical assessment to identify genetic (e.g., Prader-Willi syndrome) or endocrinologic (e.g., Cushing's syndrome) causes of their obesity. Patients also should be screened for the presence of comorbidities such as hypertension, glucose intolerance, and dyslipidemia.

The use of weight-management products in pediatric patients, as in adults, should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the expected benefits of weight loss are believed to outweigh the known and unknown risks of treatment with a particular weight-management product. Such a population might include obese pediatric patients with weight-related comorbidities.

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IV. CLINICAL ASSESSMENT OF WEIGHT-MANAGEMENT PRODUCTS IN ADULT PATIENTS

A. Phase 1 and Phase 2 Trials

Before initiating phase 3 clinical trials, the pharmacokinetics and dose-response profiles of a new weight-management product should be well-characterized. Because excess adiposity may influence a product's metabolism and disposition, the pharmacokinetics profile of a weight-management product should be examined in patients with a broad range of BMIs (e.g., 27 kg/m² to 35 kg/m²) (Cheymol 2000). To increase the likelihood of identifying the most appropriate dose for the pivotal clinical trials, early phase clinical studies should include a range of doses and be designed to identify no-effect and maximally tolerated doses. Studies should be designed to differentiate the efficacy of all the active doses versus placebo. The duration of the phase 2 trials should be sufficient to capture the maximal or near-maximal weight loss effects of the active doses. Forethought should be given to whether the product will be ultimately used in a fixed-dose or dose-titration scheme, as this dosing decision will also influence the size and duration of the studies.

Patients included in the early phase efficacy and safety studies generally should have BMIs greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² if accompanied by comorbidities. The primary efficacy endpoints should be a comparison of the mean absolute or percent change in body weight between the active-product and placebo-treated groups and the proportion of patients in each treatment group who lose greater than or equal to 5 percent of baseline weight. The effects by dose of the weight-management product on common weight-related comorbidities also should be examined and taken into account when choosing the most appropriate dose for the phase 3 studies.

B. Phase 3 Clinical Trials

1. Trial Design and Patient Populations

In general, phase 3 clinical trials examining the efficacy and safety of weight-management products should be randomized, double-blind, and placebo-controlled. The lifestyle modification programs used in the preapproval trials should be applicable to individual patients prescribed the product post-approval (i.e., programs should strike an appropriate balance between effectiveness and simplicity).

In general, patients should have or be at significant risk for weight-related morbidity and mortality. Such patients include those with BMIs greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² in the presence of comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea, cardiovascular disease).

Effort should be made to include in the studies a representative sample of patients from the various demographic, ethnic, and racial groups in which the prevalence of obesity is highest. Development programs also should include a representative sample of patients with extreme obesity (BMI greater than 40 kg/m²).

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2. *Trial Size and Duration*

The number of subjects necessary to demonstrate the efficacy of a weight-management product will be smaller than the number needed to adequately assess safety. A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment.

For example, the above sample size will provide 80 percent power to rule out with 95 percent confidence an approximately 50 percent increase in the incidence of an adverse event that occurs at a rate of 3 percent in the placebo group (i.e., 4.5 percent versus 3 percent). This sample size also should allow for efficacy and safety analyses to be conducted within important subgroups such as sex, ethnicity, and baseline BMI.

3. *Efficacy Endpoints*

a. Primary efficacy endpoint

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- Mean: The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group.
- Categorical: The proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group.

b. Secondary efficacy endpoints

Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic parameters:

- Blood pressure and pulse
- Lipoprotein lipids
- Fasting glucose and insulin
- HbA1c (in type 2 diabetics)
- Waist circumference

In clinical practice, waist circumference is used as an indirect measure of visceral fat content, which when increased is associated with an elevated risk for metabolic abnormalities such as dyslipidemia and diabetes. Because the evaluation of investigational weight-management products routinely includes assessment of changes in patients' metabolic profiles, and in some cases may involve measurement of visceral fat content by CT or MRI, waist circumference should not serve as a surrogate for visceral fat content when measured in a clinical trial investigating the efficacy of a product for weight loss. Rather, it can be a means to confirm that

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reductions in waist circumference following treatment with a weight-management product are associated with the expected improvements in metabolic parameters.

It is likely that a large portion of study subjects will be taking concomitant medications to treat weight-related comorbidities such as hypertension, type 2 diabetes, and dyslipidemia. Since weight loss is expected to improve these comorbidities, an important secondary efficacy endpoint should be the proportion of subjects treated with the weight-management product compared with placebo who have a meaningful dose-reduction or complete withdrawal of their concomitant medication. Algorithms that direct dose reduction or withdrawal of concomitant medications based on changes in levels of blood pressure, lipids, or glycemia should be included in the study protocols.

Measures of quality of life from validated instruments also can be appropriate secondary efficacy endpoints.

c. Efficacy benchmarks

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant
- The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Improvements in blood pressure, lipids, glycemia, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidities should be factored into the efficacy assessment of investigational weight-management products.

4. Standard of Care and Concomitant Medication

Overweight and obese patients enrolled in clinical studies of investigational weight-management products should receive standard of care, including medication, for comorbidities such as hypertension, dyslipidemia, and glycemic control.

5. Patients with Type 2 Diabetes

Compared with nondiabetic patients, overweight and obese patients with type 2 diabetes often respond less favorably to weight-management products and may face unique safety issues such as risk for sulfonylurea-induced hypoglycemia following weight loss (if the dose of sulfonylurea is not appropriately lowered or the drug discontinued). Therefore, sponsors should consider examining the efficacy and safety of weight-management products in trials dedicated to patients

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with type 2 diabetes. The following recommendations should be considered when designing such trials:

- In general, patients should have baseline HbA1c levels between 8 percent and 10 percent.
- Patients should be excluded if they have fasting glucose levels greater than 270 mg/dl.
- Protocols should include escape criteria for poor glycemic control.
- Protocols should include an algorithm for the lowering or elimination of oral hypoglycemia or insulin dose based on fasting glucose levels and/or HbA1c (for patients who lose clinically significant amounts of weight).
- Patient randomization should be stratified by baseline antidiabetic medication (e.g., metformin versus sulfonylurea versus a thiazolidinedione versus insulin) and baseline HbA1c level (e.g., less than or equal to 9 percent versus greater than 9 percent).
- Hypoglycemia safety should be monitored.³

C. General Safety Assessment of Weight-Management Products

To ensure that drug or biologic-induced weight loss is caused primarily by a reduction in fat content, not lean-body mass, a representative sample of study subjects should have a baseline and follow-up measurement of body composition by DEXA, or a suitable alternative.

In addition to routine safety monitoring, it may be appropriate for the development programs of some weight-management products to have specialized safety assessments. For example, products that directly interact with the 5HT receptor system, specifically the 5HT₂ receptor subtypes, probably should include evaluation of risk for cardiac valvulopathy using serial echocardiography. The development plans for centrally acting weight-management products generally should include validated assessments of neuropsychiatric function.

Assessment of the immunogenic potential of therapeutic proteins should be performed over a period of at least 6 to 12 months. If adverse events characteristic of allergic or immunologic reactions are identified, the FDA may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of an application for registration or may be conducted after approval as a postmarketing commitment, based on the overall analysis of the product's risks and benefits. The appropriate timing of such studies can be discussed with the FDA at a pre-biologics license application meeting or other similar advice meeting.

For centrally acting weight-management products, sponsors should anticipate the need to conduct preclinical and clinical studies of abuse liability. Sponsors are encouraged to discuss the design of these studies with members of CDER's Controlled Substance Staff during the early phases of product development.

³ Defining and Reporting Hypoglycemia in Diabetes: A Report from the American Diabetes Association Workgroup on Hypoglycemia, 2005, *Diabetes Care*, 28(5): 1245-9.

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The need for and details of specific safety monitoring may change as new data emerge. Sponsors are encouraged to discuss their plans for specific safety monitoring with the division during the early stages of product development.

D. Weight-Management Products Used in Combination

Two or more products may be combined into a single fixed-dosed combination when each component makes a contribution to the claimed effect or effects (21 CFR 300.50).

Before initiating long-term clinical studies with fixed-dose combinations, sponsors should conduct the appropriate preclinical and pharmacokinetics studies. (See the guidances for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* and *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*.)

We recommend that the efficacy and safety of fixed-dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-management effects of the products. We have not defined a minimum difference in weight loss between a fixed-dose combination and its individual component products that should be achieved for the combination to be considered more efficacious than either of its components when used alone. However, a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss.

Once a fixed-dose combination has been deemed more effective than its individual components, the combination can then be examined versus placebo in phase 3 trials. This approach may preclude the need to include treatment groups for the individual components of the fixed-dose combination product in late-stage preapproval trials.

The efficacy of a product combination for weight management generally will be assessed using the same factors as those applied to a single product, as defined in section IV.B.3.

E. Weight-Management Products for Patients with Medication-Induced Weight Gain

A number of drugs, notably psychotropic and some anticonvulsant agents, are associated with moderate-to-marked weight gain (Baptista and Zarate et al. 2004; Pierre and Picard 2001). In addition to increasing the risk for adverse health outcomes, medication-induced weight gain may reduce compliance with the drug responsible for the increased body weight.

Before initiating long-term clinical studies in patients with medication-induced weight gain, sponsors should rule out clinically significant drug-drug interactions and perform appropriate preclinical toxicological studies of the subject products. For details, see the guidances for industry *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and*

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Recommendations for Dosing and Labeling, and Nonclinical Safety Evaluation of Drug or Biologic Combinations.

Patients eligible for participation in trials examining the efficacy and safety of products for the treatment of medication-induced weight gain should have a documented increase in body weight of at least 5 percent within 6 months of starting a drug known to cause weight gain. Patients should have BMIs greater than or equal to 27 kg/m² with comorbidities or greater than or equal to 30 kg/m² with or without comorbidities at the time of screening.

Because most weight-management products act within the central nervous system (CNS) and many of the drugs commonly associated with moderate-to-marked weight gain are used to treat psychiatric or neurological disorders, unique issues of efficacy and safety may arise in studies of products used to treat medication-induced weight gain. For example, it would be important to demonstrate that the efficacy and safety of the medication causing the weight gain (e.g., atypical antipsychotic) was not adversely affected by a weight-management product with a CNS mechanism of action, and vice versa. These and similar issues should be taken into account when designing and determining the sample size of trials for the treatment of medication-induced weight gain.

The efficacy of a product for the treatment of medication-induced weight gain generally will be assessed using the same factors as those for weight management, as defined in section IV.B.3.

Serotonin syndrome, a potentially life-threatening condition characterized by akathisia, tremor, altered mental status, clonus, muscular hypertonicity, and hyperthermia (Boyer and Shannon 2005), has been observed in patients exposed to a single or two or more proserotonergic agents used in combination. Therefore, in general, weight-management products that act as agonists at serotonin receptors, particularly the 5-HT_{2A} subtype, should not be studied in combination with proserotonergic medications associated with weight gain.

Because of issues related to safety and possibly efficacy that are unique to the particular combinations of drugs studied, approval of a product for weight management in patients with medication-induced weight gain generally will be limited to the weight-inducing drug studied and will not apply to the drug class in which the compound is a member. For example, if a weight-management product is shown to be effective and reasonably safe in the treatment of clozapine-induced weight gain, the approved indication would be limited to clozapine-induced weight gain and would not necessarily apply to the entire class of atypical or second generation antipsychotics.

V. CLINICAL ASSESSMENT OF LONG-TERM WEIGHT-MANAGEMENT PRODUCTS IN PEDIATRIC PATIENTS⁴

Because the benefit of weight-management products should be carefully weighed against potential toxicity, particularly in the pediatric population, we anticipate that phase 3 data in adults generally will be available before a new product is studied in children.

To ensure that the most appropriate dose or doses are studied in phase 3 trials, an assessment of the pharmacokinetics of a weight-management product in pediatric patients may be appropriate before initiation of long-term clinical studies. Pharmacokinetics and dose-ranging studies generally should include patients with age- and sex-matched BMIs greater than or equal to the 95th percentile.

Trials examining the efficacy and safety of a weight-management product in pediatric patients should be randomized, double-blind, placebo-controlled, and 1 year in duration. We suggest that initial pediatric studies be limited to adolescents (i.e., 12 to 16 year olds). Eligible patients should have age- and sex-matched BMIs greater than or equal to the 95th percentile (see <http://www.cdc.gov/growthcharts>). Patients should have a documented history of failing to lose sufficient weight with lifestyle modification before enrollment into studies of a weight-management product.

We recommend that initial clinical studies include patients with one or more weight-related comorbidities such as type 2 diabetes, dyslipidemia, or hypertension. Once a satisfactory risk-benefit profile has been established in this high-risk group of patients, studies of lower risk patients can be considered. Effort should be made to recruit equal numbers of males and females and representative samples of patients from ethnic groups in which the prevalence of obesity is high.

The lifestyle modification program should continue following randomization to product or placebo and its importance emphasized at appropriate intervals throughout the trials.

Because linear growth should be taken into account when assessing changes in the body weight of children and adolescents, the primary efficacy parameter in weight-management trials of pediatric patients should be a function of the change in BMI (e.g., the mean percent change in BMI and the proportion of patients who lose greater than or equal to 5 percent of baseline BMI). Height measurements should be obtained from a wall-mounted stadiometer.

Since demonstration of adequate safety necessitates a larger sample size than demonstration of efficacy, we anticipate that the sample size of the long-term pediatric weight-management studies will be determined by considerations of the product's mechanism of action and safety profile in adults. Sponsors should discuss and justify their proposed sample size with the division before initiating the study.

⁴ For details on preclinical and pharmacokinetic evaluations for pediatric product development, see the ICH guidances for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* and *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*.

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In addition to standard safety evaluations specific to growing children (e.g., assessing Tanner stage at baseline and endpoint), studies of centrally acting weight-management products in pediatric patients also should include validated assessments of neuropsychiatric function. Other specialized safety assessments may be appropriate depending on the product's mechanism of action and its safety profile in adults.

The efficacy assessment of a weight-management product in pediatric patients will take into account the product's effectiveness in overweight and obese adults as well as the magnitude of the difference in the mean and categorical (greater than or equal to 5 percent) changes in BMI from baseline to Year 1 in pediatric patients treated with active product versus placebo.

VI. STATISTICAL CONSIDERATIONS

A. Sample Size

The number of subjects in a placebo-controlled trial should be the maximum of sample sizes calculated based on the co-primary endpoints of categorical response defined as greater than or equal to 5 percent reduction in baseline body weight after 1 year, and change from baseline weight. Calculations should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes for the calculations should represent clinically meaningful differences.

B. Preventing Missing Data from Premature Subject Withdrawal

Historically, there have been high rates of premature subject withdrawal in long-term trials of weight-management products. To allow for a true intent-to-treat (ITT) analysis, we encourage sponsors to obtain body weight measurements in all subjects who prematurely withdraw from late-stage preapproval trials near the calendar date at which they were scheduled to complete the trial (Simons-Morton and Obarzanek et al. 2006). For example, a subject who withdraws from a 12-month study after 6 months of treatment should have a body weight measurement at the time he or she would have completed 12 months of study participation.

C. Analysis Methods

Response rates should be compared between treatment groups using statistical methods appropriate for categorical data. A sensitivity analysis should be conducted that considers subjects who are treated, drop out, and do not have complete post-baseline data as treatment failures.

The analysis of (percentage) weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model. The analysis should be applied to the last observation carried forward on treatment in the modified ITT population defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. The imputation strategy should always be prespecified and should

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consider the expected dropout patterns and the time-course of weight changes in the treatment groups. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. Repeated measures analyses can be used to analyze longitudinal weight measurements but should estimate the treatment effect at the final time point. Statistical models should incorporate as factors any variables used to stratify the randomization. As important as assessing statistical significance is estimating the size of the treatment effect. If statistical significance is achieved on the co-primary endpoints, type 1 error should be controlled across all clinically relevant secondary efficacy endpoints intended for product labeling.

D. Graphical Methods

Graphical methods showing treatment effects over time for completers should be presented. Cumulative distribution plots can be useful for showing response rates for different definitions of response based on the percentage of subjects with a change value equal to or less than the value on the x-axis selected to define the positive response. Additional graphical presentations of the data to illustrate the effect of the drug are encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

VII. LABELING CONSIDERATIONS

Data on the changes in the major weight-related comorbidities are important in assessing the overall risk-benefit profile of a new weight-management product and can be included in the Clinical Studies section of the product's labeling. However, it is important to recognize that even though secondary efficacy endpoints are prespecified and the overall type 1 error rate is controlled for, that does not necessarily guarantee that all secondary endpoints will be included in labeling if the differences between active-product and placebo-treated groups are of nominal statistical significance. The clinical significance and consistency across studies of any observed differences will be important in determining whether the secondary efficacy data merit inclusion in the Clinical Studies section of the labeling.

VIII. STAND-ALONE INDICATIONS FOR THE PREVENTION OR TREATMENT OF WEIGHT-RELATED COMORBIDITIES

As mentioned earlier, weight loss through lifestyle modification is associated with improvements in blood pressure, lipid levels, glucose and insulin metabolism, and other physiometabolic endpoints. Improvements in these comorbidities are expected following drug or biologic-induced weight loss, and from a regulatory perspective, they are considered part of the weight-management indication. Thus, for a weight-management product to obtain a stand-alone indication for the prevention or treatment of type 2 diabetes, dyslipidemia, hypertension, or any other weight-related comorbidity, it should be shown that the product effectively prevents or treats the comorbidity through a mechanism that is independent of weight loss.

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IX. METABOLIC SYNDROME

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. The FDA does not necessarily consider the metabolic syndrome to represent a distinct disease entity. At present, there is no single etiological factor or central pathogenetic abnormality identified as mediating the constellation of excess visceral adiposity, abnormal lipids, elevated blood pressure, and insulin resistance that comprise the metabolic syndrome. Nonetheless, in addition to lifestyle modification, a host of drug therapies now exist to address individual or multiple components of the syndrome (e.g., lipid altering agents, antihypertensives, insulin sensitizers). Ideally, a therapeutic product intended to treat metabolic syndrome should *normalize* or improve all components of the syndrome, independent of weight loss (see section VIII), and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality.

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The North American Antiepileptic Drug Pregnancy Registry

Registry Releases Data on Six Monotherapy Drugs

The North American Antiepileptic Drug Pregnancy Registry announces the release of preliminary findings on the effects of six additional antiepileptic drugs. Previously, we only released data once it met our rigorous release criteria (lower 95% CI greater than 2.0), which is often only possible after accumulating a sample of several hundred women taking the same drug. For example, we know that sample sizes of at least 555 infants give us 80% power to identify a two-fold increase in all malformations. Since there are many AEDs that are not as popular as others, it could take many years before those samples are large enough to meet our release criteria or statistical significance. Therefore, after 11 years of enrollment, the Scientific Advisory Committee of the Registry recommended that we publish our findings on 6 drugs taken as monotherapy, even though their sample sizes are small, and only one reaches statistical significance.

We consider this a progress report. The findings shown here should not be used to predict the risk of a malformation for women taking any of these drugs, except for those based on at least 600 enrolled pregnancies (lamotrigine and carbamazepine).

The six drugs for which we have new data are phenytoin, clonazepam, gabapentin, topiramate, oxcarbazepine, and levetiracetam. The following is the data we have collected for each of these six drugs when used as monotherapy, in addition to previously released data on lamotrigine and carbamazepine.

Compound Name	Brand Name	Total Malformations	Enrolled Pregnancies	Prevalence of Malformations	95% Confidence Intervals
phenytoin	Dilantin®	10	390	2.6 %	1.2 - 4.5 %
clonazepam	Klonopin®	2	50	4.0 %	0.68 - 12.6 %
gabapentin	Neurontin®	1	127	0.8 %	0.039 - 3.8 %
topiramate	Topamax®	8	197	4.1 %	1.9 - 7.6 %
oxcarbazepine	Trileptal®	2	121	1.7 %	0.28 - 5.4 %
levetiracetam	Keppra®	4	197	2.0 %	0.65 - 4.8 %
lamotrigine ¹	Lamictal®	16	684	2.3 %	1.3 - 3.8 %
carbamazepine ²	Tegretol®	22	873	2.6 %	1.5 - 4.3 %
external controls ³	n/a	1,119	69,277	1.6%	1.5 - 1.7 %

The values in the Prevalence of Malformations column represent the rate of malformations for each specific drug. In order to understand what those numbers really mean, we must compare them to the rate of malformations for pregnancies in which the mother was not taking any antiepileptic medication. According to the Active Malformations Surveillance Program at Brigham and Women's Hospital, that rate is approximately 1.62%, after excluding malformations due to chromosomal abnormalities and genetic disorders³. In comparison, (continued on page 2)

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Registry Releases Data (continued from Page 1)

the findings in the topiramate-exposed pregnancies show a statistically significant increased rate (4.1%) across all malformations. However, the identified malformations were eight separate, common birth defects and did not show an increase for any specific abnormality. As we enroll more topiramate-exposed pregnancies, further analysis could show a much lower rate of malformations. The prevalence of malformations for clonazepam-exposed pregnancies (4.0%) appears similar to that of topiramate, but clonazepam's relatively small sample size does not produce results that are statistically significant.

As you can see in the table, the numbers in the Confidence Interval column are ranges rather than fixed values. In order to account for the role of chance, we are providing this 95% confidence interval around the prevalence values. That is, if we were to repeat our study a hundred times, the prevalence would vary, but it would be within this interval 95% of the time. Confidence intervals are important because they measure how certain we are about our results. With small sample sizes, almost any prevalence value can be explained by chance alone because the confidence intervals are wide. The larger the sample size, the narrower the confidence interval; and the narrower the confidence interval, the more certain we are about the result. For example, the confidence interval for clonazepam, which has a small sample size of 50, is very wide: 0.68-12.6%. This means that the prevalence of major malformations in clonazepam-exposed pregnancies could be as low as 0.68% or as high as 12.6%. On the other hand, the confidence interval for lamotrigine, which has a large sample size of 684, is narrow: 1.3-3.8%.

This is why we still need your help. Enrolling more women is the only way to overcome the limitations of small sample sizes, so that we can provide accurate and useful information to health care providers and the women they treat. With your continued dedication and support, we can continue to seek answers to the difficult questions facing pregnant women taking antiepileptic medications. We would like to thank everyone who has contributed thus far; we are excited to have you on board as the Registry continues to grow. Please continue to encourage any woman currently taking AEDs for any reason to call us toll free at **1-888-233-2334** to enroll in the Registry.

¹ Holmes L.B., et al. *Neurology* 2008; 70:2152-2158

² Hernandez-Diaz, S., et al. *Birth Defects Research (Part A)* 2007; 79:357.

³ Nelson K et al: *N Engl J Med* 1989; 320:19-23. We choose the findings in the Active Malformations Surveillance Program at Brigham and Women's Hospital as our comparison group because their large sample size gives their data a convincing level of statistical significance. In addition, the inclusion/exclusion criteria used in that study are the same, making the comparison even more accurate.

upcoming release of our latest research findings.

Statistics Update

Enrollment: 6,690 participants as of November 2008

Participants:

Gravidity:

1st Pregnancy: 38%
2nd Pregnancy: 30%
3rd Pregnancy: 17%
4th + Pregnancy: 16%

Education:

Some high school or less: 21%
Some college: 25%
College: 34%
Post-graduate: 21%

Ethnicity:

White: 86%
Black: 4%
Hispanic: 6%
Other: 4%

Health Insurance

Some form of insurance: 97%

Drugs Taken:

23 different monotherapies and 197 different polytherapy combinations

We need your help in recruiting Controls!

We enroll two different groups of women at the AED Pregnancy Registry. One group is case participants, who are pregnant women taking one or more anti-epileptic drugs. The other group is control participants, pregnant women not taking any AEDs. It is very important for our analyses to have a control group to compare with the women who are taking AEDs in order to better determine the risks of taking AEDs during pregnancy.

If you know of someone who can serve as a control, please ask her to call us TOLL FREE at **1-888-233-2334**. As a token of our appreciation, each participant who refers a friend or family member that enrolls as control with the Registry will be entered into a drawing to win a \$400 **American Express Gift Card**. In addition, control group members will be entered into a separate drawing to win their own \$400 American Express Gift Card. You both have a chance to win! For every woman you refer as a control, you get one raffle entry. The more women you refer, the more chances you have to win the raffle!

Children exposed to valproic acid before birth

The Genetics Unit of the MassGeneral Hospital for Children is looking for children who were exposed to the anticonvulsant drug, valproate, before birth. There has been some concern that prenatal exposure to this drug increases the risk for Autism Spectrum Disorders (ASDs) in some children. We are studying whether the effects of exposure to valproate during pregnancy depend on the child's genetic makeup (the presence of certain genes).

To participate in this study, the children must be at least 2 years of age. The research study would require only a one-day visit as an outpatient free of charge. For some children, the visit would be shorter than an entire day. Participants will receive \$100 for his/her participation, and travel expenses will be reimbursed. If you are interested in participating or would like more information, please contact **Uma Deshmukh** by calling **617-724-1252** or by e-mail at **udeshmukh@partners.org**. You can also call us at our toll-free number **1-866-354-1523**.

Medications being Studied by the AED Pregnancy Registry *:

Ativan® (lorazepam)
Carbatrol® (carbamazepine)
Celontin® (methsuximide)
Depakene® (valproic acid)
Depakote® & Depakote ER (divalproex sodium)
Diamox® (acetazolamide)
Dilantin® (phenytoin)
Felbatol® (felbamate)
Frisium® (clobazam)
Gabitril® (tiagabine)
Keppra® (levetiracetam)
Klonopin® (clonazepam)
Lamictal® (lamotrigine)
Lyrica® (pregabalin)
Mesantoin® (mephenytoin)
Milontin® (phensuximide)
Mysoline® (primidone)
Neurontin® (gabapentin)
Paradione® (paramethadione)
Peganone® (ethotoin)
phenobarbital (generic)
Phenytek® (extended phenytoin sodium)
Sabril® (vigabatrin)
Serax® (oxazepam)
Tegretol® (carbamazepine)
Topamax® (topiramate)
Tranxene® (clorazepate dipotassium)
Tridione® (trimethadione)
Trileptal® (oxcarbazepine)
Valium® (diazepam)
Xanax® (alprazolam)
Zarontin® (ethosuximide)
Zonegran® (zonisamide)

* This is not a complete list. Please call TOLL FREE **1-888-233-2334** to determine if the Registry is studying your specific medication.

The North American AED Pregnancy Registry

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Recent Publications of the Registry

Holmes L.B., Wyszynski D.F., Baldwin, E.J., Smith, C.R., Habecker, E., Glassman, L.H. Increased Frequency for Isolated Cleft Palate Among Infants Exposed To Lamotrigine During Pregnancy. *Neurology* 2008; 70:2152-2158.

Bromfield, E.B., Dworetzky, B.A., Wyszynski, D.F., Smith, C.R., Baldwin, E.J., Holmes, L.B. Valproate Teratogenicity and Epilepsy Syndrome. *Epilepsia* 2008 Jun 13 (Brief Communication).

Smith, C.R., Holmes, L.B. Recruitment of An Unexposed Control Group For A Pregnancy Registry. *Birth Defects Research (Part A)* 82:311 (2008). (Abstract)

Holmes, L.B., Smith, C.R., Hernandez-Diaz, S. Pregnancy Registries: Larger Sample Sizes Essential. *Birth Defects Research (Part A)* 82:307 (2008). (Abstract)

Holmes, L.B., Pregnancy Registries: The Importance of Inclusion and Exclusion Criteria. *Birth Defects Research (Part A)* 82:337 (2008). (Abstract)

Hernandez-Diaz, S., Smith, C.R., Wyszynski D.F., Holmes L.B. Risk of Major Malformations Among Infants Exposed to Carbamazepine During Pregnancy. *Birth Defects Research (Part A)* 2007; 79:357. (Abstract)

Who Can Participate in the Registry?

The Registry is currently enrolling pregnant women who are taking AEDs for any reason. Participating in the Registry only requires 3 telephone interviews. The first interview takes 20 minutes to complete and the next two take 5 minutes each. All information is kept strictly confidential. We are also recruiting controls, please see page 3 for details. Enrollment is open to women during any stage of pregnancy, but not after the birth of the infant. Ideally, the Registry would prefer to enroll women before they reach the 16th week of pregnancy, or before any prenatal screening. To enroll, or get more information please call the Registry TOLL FREE at **1-888-233-2334**.

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