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Draft Discussion Points and Voting Question

1. Discuss your interpretation of the available data regarding teratogenicity of topiramate, including whether you believe the data indicate an increase in the risk for oral clefts.
2. Discuss the potential strengths and weaknesses of the proposed teratogenicity risk management strategy for PHEN/TPM.
3. Taking into account the reported changes in antihypertensive therapy, discuss the clinical significance of the changes in blood pressure and heart rate in overweight and obese patients treated with PHEN/TPM versus placebo.
4. Taking into account the reported changes in antidiabetic therapy, discuss the clinical significance of the changes in HbA1c in overweight and obese patients with type 2 diabetes treated with PHEN/TPM versus placebo.
5. Discuss whether you believe the available data for PHEN/TPM warrant that a cardiovascular outcomes trial be conducted prior to approval.
6. Considering all the available data included in the application and today's discussions, do you conclude that the overall benefit-risk assessment of PHEN/TPM supports its approval for the treatment of obesity in individuals with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with weight-related co-morbidities?

Vote: Yes/No

- a. If voting "Yes" please provide your rationale and comment on the approach to post-approval risk management
- b. If voting "No" please provide your rationale and comment on what additional clinical data would be required to support approval.

**Clinical Briefing Document
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
February 22, 2012**

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

Executive Summary

On December 28, 2009, the applicant, VIVUS, Inc. submitted a New Drug Application (NDA) seeking approval of QNEXA for the treatment of obesity. QNEXA is a fixed-dose combination of proprietary formulations of phentermine hydrochloride and topiramate. The applicant has studied QNEXA, herein referred to as PHEN/TPM, using 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.

Phentermine and topiramate are licensed for use in the U.S. Phentermine hydrochloride was approved in 1959 as an appetite suppressant and is available in 15 mg to 37.5 mg tablets. 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.

In the original NDA submission, pivotal efficacy and safety data was generated in three Phase 3 studies:

- **OB-301** - a factorial designed study in obese healthy adults which demonstrated that both mid- and high-dose PHEN/TPM achieved clinically and statistically significant weight loss compared to their respective components alone, thus satisfying the combination rule cited in 21 CFR 300.50(a).
- **OB-302** - a randomized, blinded, placebo-controlled study of 1 year duration in obese adults [body mass index (BMI) ≥ 35 kg/m²] with limited weight-related co-morbidities
- **OB-303** - a randomized, blinded, placebo-controlled study of 1 year duration in overweight and obese adults (BMI ≥ 27 kg/m² and ≤ 45 kg/m²) with weight-related co-morbidities, including diabetes.

In the review of the original NDA submission, the Division of Metabolism and Endocrinology Products (DMEP) concluded that PHEN/TPM met the two efficacy benchmarks for weight loss drugs that were established in the Division's 2007 Guidance for Developing Products for Weight Management. After evaluating the safety data from the PHEN/TPM clinical development program and reviewing the safety profile of phentermine and topiramate, DMEP reviewers focused on five safety concerns: suicidality, cognitive dysfunction, metabolic acidosis, cardiovascular safety, and the potential teratogenic effect of PHEN/TPM.

These data (from the original NDA) were presented at the July 15, 2010, Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) meeting. EMDAC deliberations were notable for the safety concerns expressed by several members, particularly regarding adverse

cardiovascular effects (increased heart rate) and risk of teratogenicity. The members voted against approval of PHEN/TPM (10 to 6 with no abstentions). DMEP issued a Complete Response (CR) letter on October 28, 2010, citing as deficiencies insufficient assessment of PHEN/TPM's cardiovascular risk and teratogenic potential.

In response to the CR letter, the applicant submitted the following additional material to the NDA:

- the final study report of study **OB-305**, a Phase 3, 1-year extension study of eligible patients from applicant-selected sites from study OB-303;
- a cardiovascular (CV) risk analysis report of PHEN/TPM; and
- a review of topiramate's and PHEN/TPM's teratogenic potential.

In aggregate, the pivotal clinical data from the PHEN/TPM development program consists of one 6-month, Phase 3 factorial designed study (OB-301), two Phase 3, 1-year long studies to establish efficacy and safety (OB-302, OB-303), and one 52-week extension (OB-305) from an enriched population to provide supportive data as a 2-year cohort. The details of the make-up of the 1-year and 2-year cohorts for efficacy and safety are described in the relevant sections of this document. With respect to study OB-305, careful interpretation of the data is advised, as it represents experience from a relatively small non-randomized subgroup of patients comprising roughly a quarter of the original randomized cohort from study OB-303. Comparisons of the 1-year and 2-year data should always be interpreted in the context of these differences.

The approach to the review (which is reflected in the organization of this briefing document) was to 1) evaluate the 2-year efficacy and safety data as supportive data in the context of the previously reviewed 1-year data, 2) review the newly submitted cardiovascular data analyses, and 3) evaluate the data regarding topiramate's teratogenic potential, with a focus on risk for oral clefts (OC).

PHEN/TPM Efficacy

With regard to the efficacy benchmarks established by the Division, the following is a high-level summary of the data:

- **Mean:** High-dose PHEN/TPM recipients in study OB-302 and OB-303, and mid-dose recipients in study OB-303 achieved placebo-subtracted least squares (LS) mean reductions in weight of $\geq 5\%$. Low-dose PHEN/TPM recipients in study OB-302 did not exceed a 5% treatment difference over placebo. Mid- and high-dose PHEN/TPM recipients in study OB-305 supported the efficacy findings in the 1-year studies.
 - OB-302: low dose PHEN/TPM 3.5%; high-dose PHEN/TPM 9.4%
 - OB-303: mid-dose PHEN/TPM 6.6%; high-dose PHEN/TPM 8.6%
 - OB-305: mid-dose PHEN/TPM 7.5%; high-dose PHEN/TPM 8.7%
- **Categorical:** The percentage of PHEN/TPM recipients that achieved $\geq 5\%$ weight loss from baseline follows. For all PHEN/TPM treatment doses the percentage was at least 35%, more than double the proportion achieved with placebo treatment, and was statistically significant from placebo.

- OB-302: placebo 17.3%; low dose PHEN/TPM 44.9%; high-dose 66.7%
- OB-303: placebo 20.8%; mid-dose PHEN/TPM 62.1%; high-dose PHEN/TPM 70.0%
 - OB-305: placebo 30%; mid-dose PHEN/TPM 75.2%; high-dose PHEN/TPM 79.3%

In study OB-305, all treatment groups experienced weight gain in the second year. In individuals actively taking study drug, mean percent weight gain in the second year was greatest in the high-dose PHEN/TPM group. In individuals who lost weight in the first year, placebo-treated subjects regained a greater proportion of the weight lost in the first year compared to PHEN/TPM-treated. However, the high-dose PHEN/TPM group experienced more weight regain in the second year than the mid-dose PHEN/TPM group.

In general, PHEN/TPM recipients experienced favorable changes in weight-related comorbidity outcomes. (This was generally true of blood pressure, but those data are discussed in more detail in the cardiovascular risk assessment section in the context of other CV data, such as changes in heart rate). For example, in study OB-305, treatment with PHEN/TPM was associated with a lower incidence of new onset diabetes based on laboratory thresholds (fasting glucose ≥ 126 mg/dL or 2-hour oral glucose tolerance test (OGTT) glucose ≥ 200 mg/dL); this outcome occurred in 7%, 3.2%, and 1.7% of the placebo, mid- and high-dose groups, respectively. In study OB-305, the LS mean hemoglobin A1C (HbA1c) remained stable with PHEN/TPM treatment while HbA1c increased 0.2% points with placebo treatment. In a subgroup of individuals with diabetes at baseline participating in the 2-year study, mid- and high-dose groups had a LS mean reduction in HbA1c of 0.4% and 0.2% points, respectively, compared to no change in HbA1c in the placebo group.

High-dose PHEN/TPM-associated weight loss was accompanied by average reductions in serum triglyceride (TG) levels of 11% and 14%, average increases in high density lipoprotein lipid (HDL) of 7% and 12%, and reductions in low density lipoprotein lipid (LDL) of 7% and 6% in studies OB-303 and OB-305, respectively. Overall, the long term clinical impact of the observed modest improvements in comorbidity outcomes is uncertain, particularly in a population with higher risk of CV adverse events.

PHEN/TPM safety profile

In general, safety data from the 52-week extension study, OB-305, was consistent with the safety profile noted in the 1-year safety cohort.

An FDA analysis in 2008 of 199 pooled placebo-controlled trials of 11 antiepileptic (AED) drugs, suggested that this class of drugs is associated with an increased risk of **suicidality** (odds ratio 1.8, 95% CI: 1.2, 2.7). In the 1-year safety cohort from the PHEN/TPM development program, there were two reported adverse events of suicidal ideation (one placebo and one PHEN/TPM). There were no reported adverse events regarding suicidality in the 2-year safety cohort. The Columbia-Suicide Severity Rating Scale (C-SSRS), a tool designed to prospectively assess for suicidality, was systematically administered in all PHEN/TPM Phase 3 clinical trials.

In both the 1-year and 2-year safety cohorts, there were no suicidal attempts, suicidal behaviors, or instances of serious suicidal ideation, as assessed by the C-SSRS.

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 the 1-year safety cohort, there was a dose-related pattern of cognitive-related adverse events – i.e., disturbance in attention, memory, language. The incidence of cognitive-related adverse events in the 1-year safety cohort was 1.7%, 2.0%, 5.6%, and 7.8% in the placebo, low-dose, mid-dose, and high-dose PHEN/TPM groups, respectively, and 2.2%, 6.5%, and 5.8% in the 2-year safety cohort for the placebo, mid-dose, and high-dose PHEN/TPM groups, respectively. The most common overall adverse event related to cognitive dysfunction was disturbance in attention.

Prior clinical trials of topiramate monotherapy, as well as PHEN/TPM clinical experience, demonstrate that topiramate can cause **metabolic acidosis** in some patients through inhibition of carbonic anhydrase. In the 1-year safety cohort, approximately 30.0% of subjects treated with high-dose PHEN/TPM experienced a serum bicarbonate <21 mEq/L compared to 5.9% of subjects treated with placebo. This reduction in serum bicarbonate was also observed in the 2-year safety cohort, with 30.5% of subjects treated with high-dose PHEN/TPM with low serum bicarbonate defined as <21 mEq/L compared to 4.0% of subjects 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 in overweight and obese patients; the long-term effect of low bicarbonate is unknown within this study population.

Cardiovascular risk

At one year, mid-dose and high-dose PHEN/TPM-treated subjects experienced a mean heart rate increase of 0.6 beats per minute (bpm) and 1.6 bpm, respectively, compared to the placebo-treated subjects. A higher proportion of PHEN/TPM-treated subjects also experienced a categorical increase in heart rate compared to placebo treated subjects (>20 bpm: 13.5% mid-dose PHEN/TPM, 19.6% high-dose PHEN/TPM versus 11.9% placebo). At two years, mid-dose PHEN/TPM-treated subjects had a 0.9 bpm increase over placebo-treated subjects and high-dose PHEN/TPM-treated subjects had a 1.3 bpm increase over placebo-treated subjects. As in the 1-year safety cohort, a higher proportion of PHEN/TPM-treated subjects in the 2-year safety cohort also experienced a categorical increase in heart rate compared to placebo treated subjects (>20 bpm: 17.0% mid-dose PHEN/TPM, 25.8% high-dose PHEN/TPM versus 21.6% placebo).

The significance of the increased heart rate was further explored by the applicant by analyzing the data with regard to rate-pressure product changes, heart rate outliers, changes in night-time heart rate measured by overnight polysomnogram, and by analyzing the data across subgroups. In addition, the applicant performed a post-hoc adjudication of cardiovascular adverse events across the PHEN/TPM clinical development program.

Rate-pressure product (RPP), as an estimate of myocardial oxygen demand, showed a small reduction from baseline in the placebo (LS mean -0.13), mid-dose PHEN/TPM (LS mean -0.23) and high-dose PHEN/TPM groups (LS mean -0.18) at one year. Treatment with PHEN/TPM did not demonstrate a statistically significant treatment difference from placebo. Overnight polysomnogram and telemetry measurements in 40 obese subjects with moderate-to-severe obstructive sleep apnea showed a reduction in heart rate in both placebo and PHEN/TPM groups from baseline. However, daytime heart rate measurements demonstrated a mean heart rate increase of 6 bpm in high-dose PHEN/TPM-treated over placebo-treated subjects at Week 28.

The PHEN/TPM clinical development program was not designed to seek a cardiovascular prevention indication nor to rule out cardiovascular risk, and therefore, clinical trials were not sufficiently powered to evaluate the effect of PHEN/TPM treatment on these goals. As a result, recruitment of an appropriate at-risk population, prespecification of cardiovascular events of interest and *a priori* adjudication of major adverse cardiovascular events was not part of clinical trial conduct. However, as part of the response to the CR letter, the applicant conducted a post-hoc analysis of major adverse cardiovascular events (MACE).

The traditional MACE composite preferred for cardiovascular outcome trials is cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. This endpoint occurred in 12 subjects (5 placebo, 7 PHEN/TPM) with a hazard ratio of 0.84 (95% CI 0.26, 2.64). More liberal definitions of MACE previously considered by the FDA as valid outcome measurements such as revascularizations or hospitalization for unstable angina were extracted and analyzed and similarly resulted in very small numbers of events with nominally non-statistically significant hazard ratios less than 1.0.

The clinical significance of the observed vital sign changes and result of post-hoc analyses of MACE events in the overweight and obese population treated with PHEN/TPM is uncertain. However, it is somewhat reassuring that blood pressure and rate-pressure product changes in the PHEN/TPM groups are directionally favorable and similar to placebo. Mean heart rate increased with PHEN/TPM treatment versus placebo, and while the differences are small, they were consistent across subgroups and were observed at the end of the 2-year treatment period. To prospectively assess the effect of PHEN/TPM on cardiovascular events, the applicant has proposed a post-approval, long-term, international trial to assess the superiority of PHEN/TPM over placebo in reduction of major adverse cardiovascular events in an obese at-risk population.

Teratogenicity risk

During the initial NDA review, concern was raised regarding the teratogenic potential of topiramate based on data from the North American Antiepileptic Drug Pregnancy Registry (NAAPR). At the time (2010) in the NAAPR, topiramate monotherapy-exposed pregnancies had a higher prevalence of major congenital malformations (MCM) (3.8%, 11/289) versus an unexposed control group (1.3%, 5/372) for a relative risk of 2.8 (95% CI 1.0-8.1). Four infants exposed to topiramate had cleft lip, two (0.69%) of them were isolated which was approximately 10-fold higher than the background prevalence for isolated cleft lip cited as 0.07%. Data from

the NAAPR was added to the TOPAMAX label in 2011 to characterize the increased risk of oral clefts (OC) in infants exposed to topiramate monotherapy during the first trimester of pregnancy.

Three additional pregnancy registries have tracked human pregnancy outcomes with topiramate exposure. In 2010, The UK Pregnancy and Epilepsy Register reported a MCM rate of 3.6% from 83 pregnancies exposed to topiramate monotherapy of 200 mg and higher. Of the three reported malformations, two involved orofacial clefts. Recently, the Australian Pregnancy Register reported 31 topiramate-exposed pregnancies with 1 malformation of hypospadias for a rate of 3.2%. There is no updated information from the Israeli Pregnancy Registry since 2008 in which there was 1 MCM (1/29, 3.2%) of pulmonary artery stenosis.

Data from the Wolters Kluwer database which tracks patients' pharmacy and medical claims was evaluated for the prevalence of OC and MCM among women exposed to topiramate during pregnancy compared to several comparator groups. The results of this applicant-funded study demonstrated an unadjusted relative risk for OC of 1.47 (95% CI 0.36-6.06) for the comparison between topiramate-exposed women and female migraineurs without topiramate exposure. A second retrospective cohort study, FORTRESS, undertaken by the applicant, evaluated four healthcare databases (HealthCore, OptumInsight, Kaiser Northern California, and Thomson Reuters) for prevalence of OC and MCM in infants of women exposed to topiramate during pregnancy compared to infants of women who had previously taken antiepileptic drugs when not pregnant. The preliminary FORTRESS results demonstrated a prevalence ratio for OC in topiramate monotherapy-exposed pregnancies versus unexposed of 2.00 (95 % CI 0.71-5.68; standardized by propensity score decile and center).

The Centers of Disease Control (CDC) and the Slone Epidemiology Center analyzed data from two large case-control surveillance programs, the National Birth Defects Prevention Study and Birth Defects Study, to evaluate the risk of OC and MCM with topiramate monotherapy exposure in the first trimester. The adjusted odds ratio (OR) for MCM was 1.22 (95% CI, 0.19-13.01) in the Slone data and 0.92 (95% CI, 0.26-4.06) in the CDC data; for OC, the adjusted OR was 10.13 (95% CI, 1.09-129.21) in the Slone data and 3.63 (95% CI, 0.66-20.00) in the CDC data. The adjusted pooled OR was 1.01 (95% CI, 0.37-3.22) for MCM and 5.36 (95% CI, 1.49-20.07) for OC.

There were 34 pregnancies in the PHEN/TPM clinical development program with an average gestational age at diagnosis of 5.4 weeks. Of the 19 pregnancies carried to term, newborn examinations did not reveal any major malformations. The occurrence of 34 pregnancies in a controlled clinical development program where participation required the use of rigorous contraceptive methods and a negative pregnancy test at each study visit underscores the potential for large numbers of pregnancy exposures in the target population likely to use PHEN/TPM in a real-world setting.

In addressing this concern, the applicant submitted a Risk Evaluation and Mitigation Strategy (REMS) with Elements To Assure Safe Use (ETASU) which contraindicated the use of PHEN/TPM in women of childbearing potential. According to NHANES data from 2009-2010, 35.8 % of women in the United States are obese. In addition, the major consumers of weight

loss drugs are women of childbearing potential. With these facts in mind and upon further review of FDA regulatory considerations and practices, DMEP and the Division of Risk Management (DRISK) did not support the applicant's initial REMS proposal and recommended alternative strategies. Further details regarding the advantages and limitations across the spectrum of available REMS strategies for PHEN/TPM are presented in the DRISK briefing document.

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I. Introduction

This briefing document summarizes the efficacy and safety of QNEXA, a fixed-dose combination product of phentermine and topiramate, for the treatment of obesity. The objective is to inform the members of the Endocrinologic and Metabolic Drugs Advisory Committee in order to facilitate a discussion regarding the approvability of QNEXA. In addition, guidance is sought by the Division of Metabolism and Endocrine Products regarding strategies to evaluate and mitigate the risks associated with use of QNEXA in the overweight and obese population.

This document is divided into five sections. The first section provides general information about the QNEXA clinical development program and regulatory background regarding the components of QNEXA (phentermine and topiramate) and other weight-loss drugs. The second and third sections summarize the efficacy and safety data, respectively, from the Phase 3 studies, analyzed by 1-year and 2-year cohorts. The fourth section focuses on the cardiovascular risk assessment for QNEXA. The final section discusses the teratogenic potential of QNEXA.

II. General Background

QNEXA Product/Regulatory information

QNEXA is the proposed tradename for a combination product containing proprietary formulations of immediate-release phentermine hydrochloride beads (PHEN) and modified-release topiramate beads (TPM). QNEXA, herein referred to as PHEN/TPM, is manufactured in four fixed-dose strengths 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).

On December 28, 2009, the applicant, VIVUS, Inc., submitted a New Drug Application (NDA) to support the following proposed treatment indication:

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)*

The proposed treatment regimen starts with low-dose PHEN/TPM, up-titrating over two weeks to mid-dose PHEN/TPM, the recommended maintenance dose. Subjects not achieving 3% weight loss during the first three months are considered non-responders and according to the applicant should discontinue use of PHEN/TPM. If weight loss goals are not achieved during the first 6 months of treatment, a dose increase via the three-quarter PHEN/TPM dose to high-dose PHEN/TPM may be considered. In addition, the applicant considers low-dose PHEN/TPM as a treatment dose in some subjects based on individual treatment goals.

The primary NDA submission included data from three Phase 3 trials of efficacy and safety (see **PHEN/TPM clinical development program**, below). After reviewing these data and considering presentations by the applicant and FDA regarding efficacy and safety, the EMDAC voted against approval of PHEN/TPM (10 to 6 with no abstentions). DMEP issued a Complete Response (CR) letter on October 28, 2010, citing as deficiencies the incomplete characterization of the potential adverse cardiovascular effects (i.e., increased heart rate) and an insufficient assessment of PHEN/TPM's teratogenic potential.

In response to the CR letter, the applicant submitted the following additional material to the NDA:

- the final study report of study OB-305, a Phase 3, 1-year extension study of eligible patients from applicant-selected sites in study OB-303
- a cardiovascular risk analysis report of PHEN/TPM
- a review of topiramate's and PHEN/TPM's teratogenic potential.

Phentermine and Topiramate Product/Regulatory information

The active components of PHEN/TPM are phentermine hydrochloride (PHEN) and topiramate (TPM). Phentermine hydrochloride was approved by the FDA in 1959 as an appetite suppressant. It 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).

In 2008, members of the Peripheral and Central Nervous Systems and Psychiatric Drugs Advisory Committees met jointly to consider the safety signal for suicidality apparent in FDA analyses of data on 11 antiepileptic drugs (including topiramate). The meta-analysis of 199 controlled trials yielded an overall odds ratio for suicidality of 1.80, indicating a statistically significant increase in episodes of suicidality on treatment compared to placebo. The advisory committee agreed that the data suggested an increase in risk of suicidality with AED use and voted for communicating these risks with a Medication Guide and not a boxed warning for this drug class.

On March 4, 2011, a FDA drug safety communication was issued for TOPAMAX regarding the increased risk for oral clefts in infants exposed to topiramate in utero. The labeling was changed to reflect the new safety information regarding this risk, and topiramate was reclassified to a Pregnancy Category D. Pregnancy Category D drugs have evidence of human fetal risk based on human data but use in pregnant women may be acceptable in certain situations.

The current TOPAMAX Medication Guide lists the following (in order) as the
“Most important information I should know about TOPAMAX?”

- Eye problems
- Decreased sweating and increased body temperature
- Metabolic acidosis
- Suicidality
- Fetal toxicity

Available FDA-approved weight loss pharmacotherapies

All prescription drugs currently approved for weight loss are anorectic agents, with the exception of orlistat. Orlistat (XENICAL), a lipase inhibitor, was approved for weight loss in 1999 and as an over-the-counter weight-loss medication (trade name: ALLI) in 2007. Xenical is the only FDA-approved weight loss medication for chronic use.

Phentermine was approved in 1959 as an appetite suppressant. In the year 2009, an estimated 6.4 million phentermine prescriptions were dispensed nationally in the outpatient retail pharmacy setting. The number of dispensed phentermine prescriptions peaked during year 1996 with approximately 12 million dispensed prescriptions reflecting combination use of phentermine with fenfluramine during this time. Following publication in 1997 of the risk of cardiac valvulopathy associated with this combination fenfluramine was withdrawn from the market, and phentermine prescriptions decreased substantially. However, from 2003 to 2009, phentermine prescriptions have increased 2-fold from ~3 million to ~6 million.

With regard to use in pregnancy, all weight-loss products are being re-classified to Category X (no benefit for use in pregnancy and potential risks). This reflects clinical guidelines for weight gain during pregnancy and recommendations against weight loss, even in obese pregnant women.

III. Integrated Summary of Efficacy

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.¹ 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 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.

Guidelines for weight-management products used in combination

¹ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf

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. A minimum difference in weight loss to establish superior efficacy between a fixed-dose combination and its individual component products has not been determined.

PHEN/TPM clinical development program

PHEN/TPM clinical database

The PHEN/TPM clinical development program for obesity now consists of four Phase 3 studies, five Phase 2 studies and 11 Phase 1 studies. Approximately 3,100 adults were randomized to receive PHEN/TPM and roughly 1,500 adults were treated with PHEN/TPM for 12 months or more (Table 1).

Table 1: Number of subjects randomized in PHEN/TPM clinical development program

	Total randomized	Number of Subjects by Treatment Groups					
		PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92 or 15/100	PHEN/TPM Other doses	PHEN/TPM All doses	Placebo
Phase 1 studies	686	125	107	225	195	527	98
Phase 2 studies	355	--	--	177	--	177	178
Phase 3 studies	4510	241	605	1615	--	2461	1617
Program Total	5551	366	712	2017	195	3165	1893
Subjects enrolled in crossover studies may be counted under more than one treatment							
Source: Sponsor Table 1; Module 2.5 Clinical Overview – CR submission 17 October 2011							

PHEN/TPM Description of Phase 3 clinical trials

Three Phase 3 clinical trials, OB-301, OB-302, OB-303 form the foundation of the efficacy assessment of PHEN/TPM in overweight and obese adults with and without weight-related co-morbidities. Study OB-305, as an extension study of a selected subgroup from study OB-303, is considered supportive data.

As shown in Table 2, OB-301, -302, and -303 were randomized, double-blinded, and placebo-controlled, and included a combination of three fixed-dose formulations of PHEN/TPM. The trials varied in the number and severity of weight-related co-morbidities among subjects. The three doses studied were PHEN/TPM 15/92 mg (high-dose), PHEN/TPM 7.5/46 mg (mid-dose), and PHEN/TPM 3.75/23 mg (low-dose).

Study OB-305 was a 52-week extension study of eligible subjects from selected sites in study OB-303. Eligible subjects who elected to enroll in study OB-305 were not re-randomized but continued on the same treatment they were on at the end of study OB-303.

Table 2: Description of Phase 3 trials

Study	Treatment groups	N Randomized (OB-301, OB-302, OB-303) OR Enrolled (OB-305)	Age (years)	Population	Duration	Primary endpoint <u>Secondary/other endpoints</u>
OB-301	<ul style="list-style-type: none"> Placebo PHEN 7.5 mg PHEN 15 mg TPM 46 mg TPM 92 mg PHEN/TPM 7.5/46 mg PHEN/TPM 15/92 mg 	<ul style="list-style-type: none"> 109 109 108 108 107 107 108 	Adults ≤ 70	BMI ≥ 30 kg/m ² and ≤ 45 kg/m ² Type 2 diabetes excluded	28 weeks	<ul style="list-style-type: none"> 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
OB-302	<ul style="list-style-type: none"> Placebo PHEN/TPM 3.75/23 mg PHEN/TPM 15/92 mg 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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

Study	Treatment groups	N Randomized (OB-301, OB-302, OB-303) OR Enrolled (OB-305)	Age (years)	Population	Duration	Primary endpoint <u>Secondary/other endpoints</u>
						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
OB-305 Extension of OB-303	<ul style="list-style-type: none"> Placebo PHEN/TPM 7.5/46 mg PHEN/TPM 15/92 mg 	<ul style="list-style-type: none"> 227 154 295 	Adults ≤70	BMI ≥ 27 kg/m ² and ≤ 45 kg/m ² Two or more weight-related co-morbidities	108 weeks	Weight loss at 108 weeks <u>Secondary</u> <ul style="list-style-type: none"> Absolute weight loss % with 10%, 15%, 20% weight loss Δ in waist circumference <u>Other</u> Δ in 1° and 2° EP from Week 56 to 108, Δ in BP, lipids, fasting serum glucose, HbA1c, insulin, glucose and insulin by OGTT, Framingham risk score, time to T2DM onset

The primary efficacy endpoints for the four Phase 3 trials were percent weight loss at Week 28, Week 56, or Week 108 and percentage of subjects with at least 5% weight loss at Week 28, Week 56, or Week 108. 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 subjects with at least 10% weight loss at Week 28, Week 56, or Week 108 and percentage of subjects with at least 15%, and 20% weight loss at Week 108 (OB-305)
- Change in waist circumference from baseline to Week 28, Week 56, or Week 108
- 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) or Week 108 (OB-305)

Other efficacy endpoints included changes from baseline in:

- Framingham 10-year risk assessment
- Lipids
- HbA1c (OB-301, OB-303, OB-305)
- 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, OB-305)
- Insulin resistance parameters and fasting insulin (OB-303, OB-305)
- SF-36 scores (OB-303, OB-305)
- 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. Diabetic patients 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
- Subjects with a creatinine clearance < 60 ml/min were excluded. No lower limit on BMI was established for subjects with diabetes.

OB-305: In order to be considered eligible for study OB-305, all of the following criteria must have been met:

- Study site was selected for participation based on number of eligible subjects and Good Clinical Practice (GCP) site compliance
- Completion of study OB-303 on treatment and compliance with all protocol requirements;
- Written informed consent;
- For female subjects of childbearing potential, use of adequate contraception, defined as a double-barrier method, stable hormonal contraception plus single barrier, or tubal ligation. Female subjects were considered to be of childbearing potential unless they were ≥ 55 years of age with spontaneous amenorrhea for at least 1 year or had a documented follicle-stimulating hormone level 40 IU/L or had a hysterectomy or bilateral oophorectomy; and
- Willingness and ability to comply with scheduled study visits, treatment plan, laboratory tests, and other study procedures.

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

Subjects who met any one of the following criteria were ineligible for participation in study OB-305:

- BMI ≤ 22 kg/m² at the completion of study OB-303
- Off study drug at the completion of study OB-303 for longer than 4 weeks continuously due to an event-driven drug holiday, or off study drug with no plans to restart;
- Development of any condition during study OB-303 that, in the opinion of the investigator, would contraindicate the administration of study drug, affect compliance, interfere with study evaluations, or confound the interpretation of study results; or
- Participation in formal weight loss program

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 subjects 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.

Treatment of diabetes

Metformin was suggested as the initial therapy for newly emergent type 2 diabetes unless contraindicated in a specific individual. Insulin secretagogues, including sulfonylureas and meglitinides, either alone or in combination with other medications, were reserved for subjects who could not achieve adequate control with other modes of treatment. Insulins, incretins, and thiazolidinediones were prohibited, and subjects requiring treatment with these medications were discontinued from the trial.

Subjects with consistently elevated fasting blood glucose values initiated therapy with antidiabetic medications, increased the dosage of existing medication, or added an additional agent. Subjects with 2 or more fasting glucose values exceeding 200 mg/dL in daily glucose

monitoring logs the week prior to a study visit were considered appropriate for concomitant medication adjustment. Subjects whose fasting blood glucose remained greater than 240 mg/dL after increasing their medications for glycemic management at each of 3 sequential visits, or whose blood glucose was not adequately controlled with the concomitant treatments allowed were discontinued from study treatment and referred back to their primary healthcare provider for additional glycemic management. Subjects could continue attending study visits off study medication, and if glycemic control was re-established without requiring excluded medications, they could be restarted on treatment.

During treatment, subjects with fasting blood glucose values less than 72 mg/dL on 2 or more occasions, or who experienced any signs or symptoms associated with hypoglycemia, were to have their glycemic treatment doses reduced or discontinuation of antidiabetic therapy considered if dose reductions were deemed inadequate to alleviate symptoms. When discontinuing medications, sulfonylureas were discontinued first, followed by meglitinides, α -glucosidase inhibitors and/or DPP4 inhibitors, and finally metformin.

Treatment of elevated blood pressure

For subjects whose blood pressure required management, antihypertensive therapy should have been initiated with ACE inhibitors or angiotensin receptor blockers. If these medications were already present, calcium channel blockers, beta-blockers, or thiazide diuretics may have been added. Subjects whose blood pressure exceeded 160/100 mmHg on 3 consecutive visits and who have undergone dose increases or the addition of antihypertensive medications over each of 3 visits, were to be discontinued from study treatment and referred back to their primary healthcare provider for more intensive management. Subjects may have continued attending study visits off study medication, and if blood pressure control was re-established without requiring excluded medications, subjects may have been restarted on treatment.

For subjects with blood pressure drops below 110/70 mmHg or who exhibited symptoms associated with low blood pressure during the trial, concomitant antihypertensive agents should have been withdrawn or doses should have been reduced. For this trial, it was recommended that diuretics (nonpotassium-sparing) be the first medications reduced or withdrawn followed by beta blockers, calcium channel blockers, and lastly, ACE inhibitors or angiotensin receptor blockers.

Randomization and stratification

Requirements for randomization and receiving study drug included no clinically significant abnormalities on baseline physical exam, electrocardiogram (ECG) and laboratory results. Laboratory values had to be within normal limits, defined as follows: serum bicarbonate: 21-33 mEq/L, AST and ALT $<2.5\times$ ULN, TSH $\leq 1.5\times$ ULN. Urine drug screen urine pregnancy test were required to be negative. In study OB-301, subjects 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 subjects 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 subjects 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 subjects were to be male.

OB-303 subjects 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 subjects were to be male.

OB-305 subjects included only eligible subjects from selected sites who completed study OB-303 on treatment. Subjects were not re-randomized at the end of study OB-303, but continued on the same double-blind treatment taken at the end of study OB-303.

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). During the titration period, doses were increased at weekly intervals for 4 weeks until the specified dose was reached.

Study OB-305, was a 52-week extension study of eligible subjects from selected sites from study OB-303. Eligible subjects were not re-randomized at the end of study OB-303, but continued on the same treatment taken at the end of study OB-303. Subjects who had their dose down-titrated in study OB-303 due to a tolerability issue were permitted to have their dose up-titrated to the original randomized dose during this extension study. However, dose up-titration was only performed if requested by the subject and if the investigator agreed that it was the appropriate course of action.

In all trials, if adverse events occurred that caused subjects 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 subjects from the study. Dose interruptions longer than 7 days were possible with agreement from the medical monitor. Subjects 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. Subjects 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 subjects using the LEARN Program for Weight Management developed by Kelly Brownell, PhD. Subjects were provided with a LEARN manual, and site personnel were encouraged to discuss the material at subjects' regularly scheduled visits.

Analysis populations

In studies OB-302 and -303, the Intent-to-Treat (ITT) set was defined as all randomized subjects 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. In study OB-305, the ITT Set was defined as all subjects who received at least one dose of study drug in the OB-305 study. The ITT Set was the primary analysis set for efficacy summaries.

The Modified ITT (MITT) set was identical to the ITT set except that it only included subjects with a post-dose assessment of body weight within 7 days of the last dose of study drug.

The Safety Set was defined as all randomized subjects who received at least one dose of study drug in this study and was the primary analysis set for safety summaries.

Description of subject cohorts

Below is a description of the studies/cohorts referred to in this section. Please note, that study OB-301 will not be discussed further in this briefing document. OB-301 was a factorial designed study in obese healthy adults which demonstrated that both mid- and high-dose PHEN/TPM achieved clinically and statistically significant weight loss compared to their respective components alone, satisfying the combination rule set forth in 21 CFR 300.50(a).

- Study OB-302: This cohort consists of all subjects who were randomized in study OB-302.
- Study OB-303: This cohort consists of all subjects who were randomized in study OB-303.
- One-year pooled Phase 3 cohort: This cohort consists of all subjects who were randomized to the pivotal Phase 3 studies OB-302 and OB-303.
- Study OB-305: This cohort comprises all the subjects who entered study OB-305 from selected sites in study OB-303, the 1-year extension study to OB-303. Data presented for these subjects summarizes the 2-year treatment period (OB-303 and OB-305).

Statistical considerations

Baseline for studies OB-302, OB-303, and the pooled 1-year Phase 3 cohort was defined as the last measurement obtained on or before the first dose of double-blind study drug. For study OB-305, baseline was defined as the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303.

The primary endpoint for studies OB-302, OB-303, and the 1-year Phase 3 cohort was Week 56 with last observation carried forward (LOCF) and for study OB-305 Week 108 with LOCF.

For subjects in the ITT Set who did not return to the clinic for Week 56/Week 108 assessments, the LOCF convention was used to impute data forward to the Week 56 or Week 108 time point. For determination of the LOCF measurement, the following algorithm was used:

- For subjects who completed the study or terminated early but returned for the Week 56 or 108 measurements, the Week 56 or 108 measurements were used.

- For subjects who terminated early from the study and did not provide Week 56 or 108 measurements, the last available measurement (as determined by measurement date) was used.
- For subjects in the Modified ITT Set, a similar approach was used to identify the Week 56 or Week 108 with LOCF values with the additional requirement that only observations obtained while the subject was actively taking study drug or within 7 days of the last dose were considered for the LOCF identification.

Analysis of the first primary efficacy variable, percent weight loss with LOCF, was performed using an ANCOVA model with treatment and gender as fixed effects and baseline weight as a covariate for study OB-302. Diabetic status was also included as a fixed effect in the ANCOVA model for the analysis of percent weight loss for study OB-303 and study OB-305. In the 1-year Phase 3 cohort analysis of the first primary efficacy variable, percent weight loss, was performed using an ANCOVA model with treatment, study, and gender as fixed effects and baseline weight as a covariate.

Least-squares means, corresponding standard errors, two-sided 95% confidence intervals, and two-sided p-values for the within-group percent weight loss within each treatment group were presented. For each between-treatment comparison of interest, the difference in LS means, corresponding standard error, two-sided 95% confidence interval, and two-sided p-value were derived from the ANCOVA model. Analysis of the second primary efficacy variable, percentage of subjects with at least 5% weight loss at endpoint, was performed using a logistic regression model with treatment and gender as fixed effects and baseline weight as a covariate. Diabetic status was also included as a fixed effect in the logistic regression model for the categorical analysis of weight loss for studies OB-303 and OB-305. For each between-treatment comparison of interest, the estimated odds ratio, standard error, 95% Wald confidence interval, and p-value were presented.

Subject demographics

The majority of the subjects in the 1-year PHEN/TPM studies (OB-302 and OB-303) and 52-week extension study (OB-305) were middle-aged, Caucasian women (Table 3). Approximately 17% had a history of depression. Roughly a third of subjects had extreme obesity, BMI ≥ 40 kg/m². All of the studies occurred in the United States.

Study OB-302 permitted enrollment of subjects with BMI's of 45 kg/m² and higher but excluded subjects with type 2 diabetes or uncontrolled weight-related co-morbidities. Study OB-303, and therefore study OB-305 as its extension, sought to include subjects with weight-related co-morbidities and limited the BMI inclusion criteria. These differences in study populations explain the contrast between the studies regarding BMI, fasting serum glucose, lipid parameters, and blood pressure at baseline.

Table 3: Demographic and Baseline Characteristics – OB-302 and OB-303 (randomized set), OB-305 (safety set)

Parameter	Study OB-302 N=1267	Study OB-303 N=2487	Study OB-305 N=675
Age (years)			

Parameter	Study OB-302 N=1267	Study OB-303 N=2487	Study OB-305 N=675
n	1267	2487	675
Mean (SD)	42.6 (11.8)	51.1 (10.44)	51.9 (10.2)
Gender n (%)			
Female	1050 (82.9)	1737 (69.8)	448 (66.4)
Male	217 (17.1)	750 (30.2)	227 (33.6)
Race n (%)			
Caucasian	1013 (80.0)	2140 (86.0)	576 (85.3)
African	225 (17.8)	292 (11.7)	89 (13.2)
Asian	6 (0.5)	22 (0.9)	6 (0.9)
American Indian or Alaskan native	15 (1.2)	18 (0.7)	3 (0.4)
Native Hawaiian or other Pacific Islander	5 (0.4)	7 (0.3)	3 (0.4)
Other	16 (1.3)	25 (1.0)	4 (0.6)
Weight (kg)			
n	1264	2485	675
Mean (SD)	116.1 (21.2)	103.1 (17.9)	101.7 (18.7)
BMI (kg/m²)			
n	1264	2485	675
Mean (SD)	42.1 (6.2)	36.6 (4.5)	36.1 (4.7)
LDL-C (mg/dL)			
n	1263	2480	675
Mean (SD)	121.0 (31.4)	123.1 (35.4)	122.1 (35.2)
HDL-C (mg/dL)			
n	1264	2485	675
Mean (SD)	49.8 (12.2)	48.9 (13.6)	49 (13.6)
Fasting serum glucose (mg/dL)			
n	1261	2476	674
Mean (SD)	93.2 (9.1)	106.1 (22.2)	109.2 (24.4)
Hemoglobin A1c (%)			
n	ND	2478	675
Mean (SD)	ND	5.9 (0.76)	6.0 (0.88)
Systolic blood pressure (mmHg)			
n	1264	2485	675
Mean (SD)	122.0 (11.4)	128.4 (13.5)	127.8 (13.4)
Diastolic blood pressure (mmHg)			
n	1264	2485	675
Mean (SD)	77.4 (7.7)	80.6 (9.1)	80.0 (9.1)
Heart rate (bpm)			
n	1264	2485	675
Mean (SD)	73.0 (9.2)	72.3 (10.0)	72.0 (10.2)
Non-smoker n (%)^[1]	830 (65.7)	1476 (59.4)	399 (59.1)
Subjects with n (%)^[1]			
History of depression	202 (16.0)	425 (17.1)	132 (19.6)
History of MI	5 (0.4)	37 (1.5)	12 (1.8)
History of hypertension	310 (24.5)	1710 (68.8)	345 (51.1) ^[2]
History of dyslipidemia	244 (19.3)	1421 (57.2)	233 (34.5) ^[2]
Type 2 diabetes	0	393 (15.8)	145 (21.5) ^[2]
Applicant's Table 5, Pg 49 OB-302 CSR, Table 5, Pg 57, Table 14.1.8, Pg 21 OB-303 CSR, Table 4, Pg 53 OB-305 CSR ND: Not done			

Parameter	Study OB-302 N=1267	Study OB-303 N=2487	Study OB-305 N=675
^[1] Percentage calculated using the number of subjects in the safety set in the denominator (study OB-302 N=1264, OB-303 N=2485, ^[2] % at the start of OB-303 with the condition			

Subject disposition

- 1-year Phase 3 cohort

Of the 3,754 randomized adults in the 1-year pooled Phase 3 studies (OB-302, OB-303), 2,222 (59.2%) subjects completed all study visits on study drug and 1,527 (40.7%) subjects discontinued study drug (Table 4). A higher percentage of subjects in the PHEN/TPM groups compared to the placebo group completed all study visits on study drug (placebo, 53.4%; PHEN/TPM total, 63.1%). The most common reasons for discontinuation of study drug were adverse event (13.1%), loss to follow-up (10.6%), and withdrawal of consent (10.5%). A higher percentage of subjects in the PHEN/TPM groups than in the placebo group discontinued study drug due to an adverse event. A higher percentage of subjects in the placebo group than in the PHEN/TPM groups discontinued study drug for reasons of loss to follow-up, withdrawal of consent, and lack of efficacy.

Table 4: 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 all study visits on study drug	805 (53.4)	138 (57.3)	344 (69.1)	935 (62.0)
Study drug discontinuation	701 (46.5)	102 (42.3)	154 (30.9)	570 (37.8)
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 3, Pg 39 ISE – CR submission 10/17/11 Data from studies OB-302, and OB-303				

- Study OB-305

Of the 2,487 subjects randomized in study OB-303, 1,542 (62%) completed study OB-303 on study drug, however all sites were not selected to participate in study OB-305 and therefore, only 866 subjects (35%) from the selected sites were eligible to participate in study OB-305, 676 (27%) enrolled in study OB-305, and 568 (23%) completed study OB-305 on study drug (Table 5). The table below is taken from the FDA statistical reviewer's briefing document. For further details please refer to the full statistical review included in this briefing package.

Therefore, it is important to consider when interpreting the results of study OB-305 that the results of study OB-305 constitute roughly a quarter of the originally randomized group in study OB-303.

Table 5: Subject disposition – OB-303, OB-305

	Placebo N=994 n (%)	PHEN/TPM 7.5/46 mg N=498 n (%)	PHEN/TPM 15/92 mg N=995 n (%)	Total N=2487 n (%)
Randomized in OB-303	994 (100.0)	498 (100.0)	995 (100.0)	2487 (100.0)
Completed OB-303 on study drug all sites	634 (63.8)	344 (69.1)	564 (56.7)	1542 (62.0)
Eligible to enroll in OB-305 at selected sites	327 (32.8)	194 (39.0)	345 (34.7)	866 (34.8)
Enrolled in study OB-305	227 (22.8)	154 (30.9)	295 (29.6)	676 (27.2)
Completed all study visits on study drug	196 (19.7)	127 (25.5)	245 (24.6)	568 (22.8)
Source: FDA statistical review of OB-305				

Of the 190 eligible subjects not participating in study OB-305, only three had a BMI ≤ 22 kg/m² which excluded them from participation (1 placebo, 2 high-dose PHEN/TPM). Data on the specific reasons the remaining 187 eligible subjects decided against participation in the 52-week extension study was not collected. However, the subjects treated with PHEN/TPM in this group had a higher proportion of treatment-emergent events (96.7%) compared to their counterparts that elected to participate (86.4%). Of the 676 enrolled subjects, one subject in the mid-dose PHEN/TPM group discontinued prior to receiving study drug, 568 of 675 (84%) completed all study visits on study drug, and 108 of 675 (16%) discontinued study drug with the largest proportion of study drug discontinuations occurring in the mid-dose PHEN/TPM treatment group. Of note, 20 (6.8%) high-dose PHEN/TPM treated subjects were lost-to-follow-up compared to only 4 (1.8%) placebo-treated and 4 (2.6%) mid-dose PHEN/TPM-treated subjects.

Table 6: Subject disposition – OB-305 – Enrolled set

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 mg N=154 n (%)	PHEN/TPM 15/92 mg N=295 n (%)
Eligible subjects who elected not to enroll in OB-305 ^[1]	100	40	50
Enrolled in study OB-305	227 (100.0)	154 (100.0)	295 (100.0)
Completed study visits	197 (86.8)	129 (83.8)	248 (84.1)
Completed all study visits on study drug	196 (86.3)	127 (82.5)	245 (83.1)
Discontinued	31 (13.7)	27 (17.5)	50 (16.9)

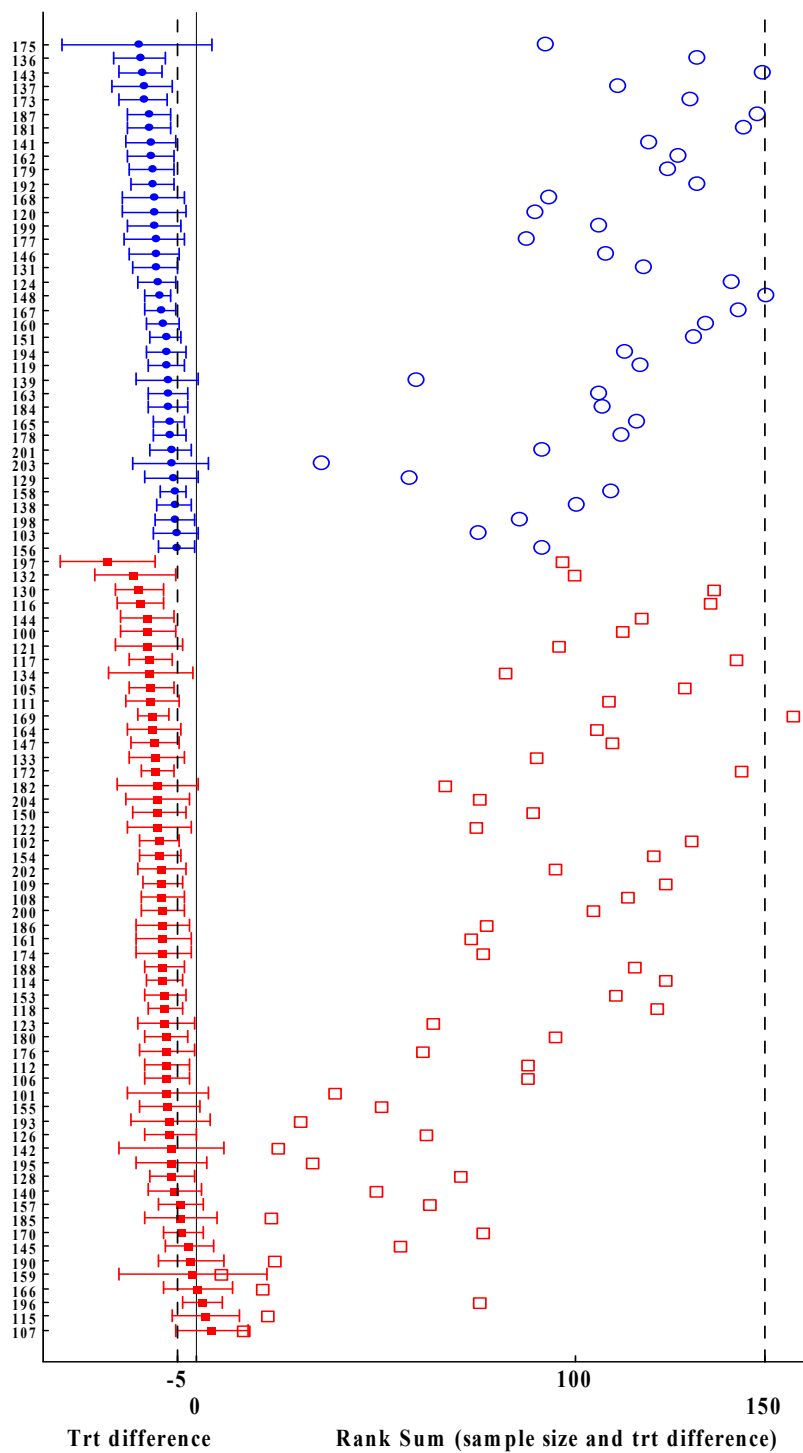
	Placebo N=227 n (%)	PHEN/TPM 7.5/46 mg N=154 n (%)	PHEN/TPM 15/92 mg N=295 n (%)
study drug			
Adverse event	7 (3.1)	7 (4.5)	13 (4.4)
Lost to follow-up	4 (1.8)	4 (2.6)	20 (6.8)
Withdrew consent	7 (3.1)	9 (5.8)	11 (3.7)
Lack of efficacy	3 (1.3)	1 (0.6)	0
Protocol non-compliance	3 (1.3)	1 (0.6)	1 (0.3)
Requirement for restricted medication	2 (0.9)	0	1 (0.3)
Pregnancy	1 (0.4)	0	1 (0.3)
Other	4 (1.8)	4 (2.6)	3 (1.0)
Source: Table 3, Pg 51, OB-305 CSR ^[1] Eligible subjects include all subjects who completed Study OB-303 on study medication at sites participating in study OB-305			

Study OB-305 Site selection

Of the 93 sites participating in study OB-303, 36 were selected to participate in study OB-305 by the applicant. The applicant reported that the number of eligible subjects and GCP compliance of sites were used as criteria for site selection to ensure that there were a statistically appropriate number of subjects to provide reliable assessment of longer term safety and efficacy data.

The FDA statistical reviewer evaluated the sample sizes and treatment difference between high-dose PHEN/TPM and placebo at Week 56 by OB-303 study site. Figure 1 plots the sites by treatment difference and rank sum. The rank sum was calculated using sample size and treatment difference. The sites listed in blue were selected for participation in OB-305; sites listed in red were not selected. The percent body weight loss difference between treatments was at least 5% for all 36 selected sites, while all 10 sites with less than 5% body weight loss difference from placebo were not selected. Therefore, the results observed in study OB-305 are considered by this reviewer to be from an enriched population and therefore, best-case scenario based on the selected group of subjects.

Figure 1: Treatment difference between high-dose PHEN/TPM and placebo at Week 56 ITT (study OB-303) by site (blue included in OB-305/red not included) and rank sum of treatment difference and sample size



Source: Figure provided by FDA statistical reviewer

Weight loss efficacy at 1-year (OB-302 and OB-303) and 2-years (Study OB-305)

In all Phase 3 studies, PHEN/TPM resulted in a placebo-subtracted LS mean percent weight loss of at least 5% and/or a higher proportion of subjects achieving 5% or greater weight loss compared to placebo thus achieving the established efficacy benchmarks set forth by the FDA for weight loss.

In the pooled 1-year Phase 3 cohort, the placebo-subtracted LS mean percent weight loss for mid- and high-dose PHEN/TPM was 6.7% and 8.9%, respectively (Table 7). Sixty-two percent and 69% of the subjects treated with mid- and high-dose PHEN/TPM, respectively lost at least 5% of baseline body weight compared to 20% of subjects treated with placebo (Table 8).

Treatment with mid-and high-dose PHEN/TPM at two years resulted in placebo-subtracted LS mean percent weight loss of 7.5% and 8.7%, respectively. Seventy-five percent and 79% of subjects treated with mid-dose and high-dose PHEN/TPM, respectively, lost at least 5% of baseline body weight compared to 30% of subjects treated with placebo.

Although there was a statistically significant treatment difference of approximately 2% LS mean percent weight loss and categorical weight loss between mid- and high-dose PHEN/TPM treatment in study OB-303 at Week 56, there was no statistically significant difference between mid- and high-dose PHEN/TPM in LS mean percent weight loss or categorical achievement of >5% weight loss in study OB-305 at Week 108. It should be noted that although there was a lack of statistical difference at Week 108, treatment with high-dose PHEN/TPM resulted in additional, albeit small, amounts of weight loss.

Table 7: Percent weight loss at Week 56 and Week 108 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 (SE) difference	95% CI	p-value
OB-302 [1] Week 56	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] Week 56	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
					Difference between PHEN/TPM doses		
	High vs mid PHEN/TPM	--	--	--	2.0 (0.4)	(1.2, 2.8)	<0.0001
Pooled OB-302, OB-303 [3] Week 56	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
OB-305 [2] Week 108	Placebo	227	101.1 (18.85)	2.5 (6.76)	--	--	--
	PHEN/TPM 7.5/46	153	102.2 (18.37)	10.4 (8.04)	7.5 (0.80)	(6.0, 9.1)	<0.0001
	PHEN/TPM 15/92	295	101.9 (18.87)	11.4 (8.30)	8.7 (0.67)	(7.4, 10.0)	<0.0001
					Difference between PHEN/TPM doses		
	High vs mid PHEN/TPM	--	--	--	1.2 (0.76)	(-0.3, 2.7)	0.1189

Source: Applicant's Table 8, Pg 53, OB-302, CSR; Table 9, Pg 64 OB-303 CSR; Table 13, Pg 55 ISE; Table 8, Pg 59, OB-305 CSR

[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 8: Summary of the percentage of subjects with $\geq 5\%$, $\geq 10\%$, $\geq 15\%$ at Week 56 or Week 108 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 [1] Week 56	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 [2] Week 56	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
			PHEN/TPM dose difference†		PHEN/TPM dose difference†		PHEN/TPM dose difference†
	High vs Mid PHEN/TPM	--	7.9‡	--	10.3‡‡	--	9.5‡‡‡
Pooled OB-302, OB-303 [3] Week 56	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
OB-305 [2] Week 108	Placebo	30.0%	--	11.5%	--	6.6%	--
	PHEN/TPM 7.5/46	75.2%**	45.2	50.3%**	38.8	24.2%**	17.6
	PHEN/TPM 15/92	79.3%**	49.3	53.9%**	42.4	31.9%**	25.3
			PHEN/TPM dose difference†		PHEN/TPM dose difference†		PHEN/TPM dose difference†
	High vs Mid PHEN/TPM	--	4.1	--	3.6	--	7.7
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, Applicant's Table 10, Pg 61 OB-305 CSR EP: Endpoint †High-dose minus mid-dose PHEN/TPM *p<0.05 **p<0.0001 compared to placebo ‡p<0.005 ‡‡p=0.0001 ‡‡‡p<0.0001 comparison between high-dose and mid-dose PHEN/TPM [1] Two-sided p-value are from a logistic regression model with treatment and gender as fixed effects and baseline weight as a covariate. [2] Two-sided p-value are from a logistic regression model with treatment, gender, and diabetic status as fixed effects and baseline weight as a covariate. [3] Two-sided p-value are from a logistic regression model with treatment, study, and gender as fixed effects and baseline as a covariate.							

Secondary and other endpoints

Change in LS mean percent and categorical weight loss over time – Study OB-305

In study OB-305, at Weeks 28, 56, and 108 with LOCF, the LS mean percent weight loss and categorical weight loss was statistically greater in the PHEN/TPM-treated versus the placebo-treated groups (Table 9).

There was a statistically significant difference in percent and categorical weight loss between high- and mid-dose PHEN/TPM at Week 56, however, at Week 108, the treatment difference was smaller and lacked statistical significance. This same pattern of weight loss was noted in subjects who were actively taking study drug (MITT non-LOCF) (Table 10).

Table 9: Study OB-305: LS mean percent weight loss from baseline over time – ITT LOCF

Treatment comparison	Wk 28 (LOCF)		Wk 56 (LOCF)		Wk 108 (LOCF)	
	LS mean % (SE) difference	p-value	LS mean % (SE) difference	p-value	LS mean % (SE) difference	p-value
PHEN/TPM 7.5/46 vs placebo	6.2 (0.6)	<0.0001	7.8 (0.8)	<0.0001	7.5 (0.8)	<0.0001
PHEN/TPM 15/92 vs placebo	8.4 (0.5)	<0.0001	10.0 (0.6)	<0.0001	8.7 (0.7)	<0.0001
PHEN/TPM 15/92 vs PHEN/TPM 7.5/46	2.2 (0.6)	0.0001	2.3 (0.7)	0.0019	1.2 (0.8)	0.1189
Source: Applicant's Post-text Table 14.2.2, OB-305 CSR, Pg 61 Baseline defined as the last measurement obtained on or before the first dose date of double-blind study medication of OB-303 LS mean, SE, 95% CI, and two-sided p-value are obtained from an ANCOVA model with treatment, gender, and diabetic status as fixed effects, and baseline weight as a covariate						

Table 10: Study OB-305: LS mean percent weight loss from baseline over time – MITT non-LOCF

Treatment comparison	Wk 28 (MITT non-LOCF)			Wk 56 (MITT non-LOCF)			Wk 108 (MITT non-LOCF)		
	N	LS mean % (SE) difference	p-value	N	LS mean % (SE) difference	p-value	N	LS mean % (SE) difference	p-value
PHEN/TPM 7.5/46 vs placebo	149 226	6.3 (0.60)	<0.0001	147 224	7.7 (0.78)	<0.0001	125 196	7.1 (0.88)	<0.0001
PHEN/TPM 15/92 vs placebo	288 226	8.5 (0.51)	<0.0001	285 224	10.1 (0.65)	<0.0001	240 196	8.6 (0.74)	<0.0001
PHEN/TPM 15/92 vs PHEN/TPM 7.5/46	288 149	2.1 (0.58)	0.0002	285 147	2.4 (0.75)	0.0015	240 125	1.5 (0.85)	0.0879
Applicant's Post-text Table 14.2.4, Pg 103, OB-305 CSR Baseline defined as the last measurement obtained on or before the first dose date of double-blind study medication of OB-303 LS mean, SE, 95% CI, and two-sided p-value are obtained from an ANCOVA model with treatment, gender, and diabetic status as fixed effects, and baseline weight as a covariate									

As demonstrated in the tables below, at Weeks 28, 56, and 108 the percentage of subjects with 5% weight loss from baseline was statistically greater in the PHEN/TPM-treated versus the placebo-treated group (ITT LOCF) (Table 11).

A treatment comparison at Week 56 between mid- and high-dose PHEN/TPM groups showed a statistically significant difference in the percentage of subjects with 5% weight loss in the ITT

LOCF population and MITT population non-LOCF, however, at Week 108, these differences were smaller and no longer statistically significant.

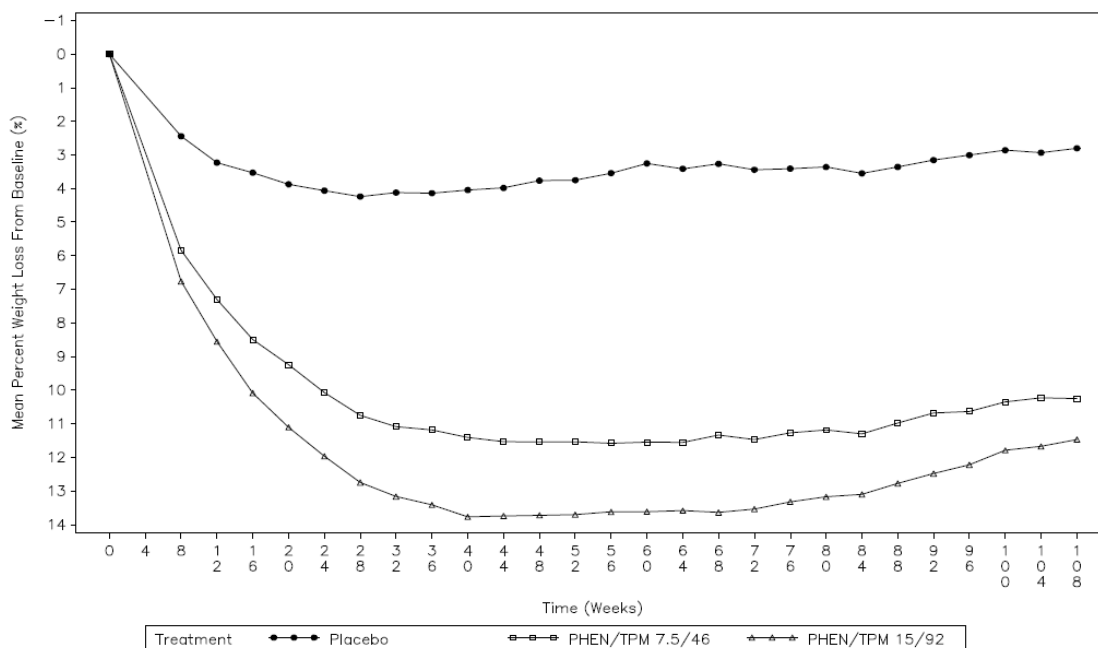
Table 11: Percent achieving $\geq 5\%$ weight loss over time and between treatment comparisons – ITT LOCF and MITT non-LOCF

	Wk 28 (LOCF)				Wk 56 (LOCF)				Wk 108 (LOCF)			
	% on PHEN/TPM	% on pbo	Odds Ratio (SE)	p-value	% on PHEN/TPM	% on pbo	Odds Ratio (SE)	p-value	% on PHEN/TPM	% on pbo	Odds Ratio (SE)	p-value
PHEN/TPM 7.5/46 vs placebo	84.3	37.0	9.0 (2.39)	<0.0001	79.7	31.7	8.7 (2.21)	<0.0001	75.2	30.0	7.0 (1.68)	<0.0001
PHEN/TPM 15/92 vs placebo	89.8	37.0	16.0 (3.88)	<0.0001	87.1	31.7	16.9 (4.04)	<0.0001	79.3	30.0	9.4 (2.0)	<0.0001
PHEN/TPM 15/92 vs PHEN/TPM 7.5/46			1.8 (0.53)	0.0562			2.0 (0.54)	0.0150			1.4 (0.32)	0.2169
	Wk 28 (MITT non- LOCF)				Wk 56 (MITT non-LOCF)				Wk 108 (MITT non- LOCF)			
	% on PHEN/TPM	% on pbo	Odds Ratio (SE)	p-value	% on PHEN/TPM	% on pbo	Odds Ratio (SE)	p-value	% on PHEN/TPM	% on pbo	Odds Ratio (SE)	p-value
PHEN/TPM 7.5/46 vs placebo	84.6	36.7	9.4 (2.53)	<0.0001	78.9	31.7	8.2 (2.10)	<0.0001	73.6	30.1	6.3 (1.64)	<0.0001
PHEN/TPM 15/92 vs placebo	89.9	36.7	16.3 (4.02)	<0.0001	87.7	31.7	18.0 (4.43)	<0.0001	81.3	30.1	10.5 (2.44)	<0.0001
PHEN/TPM 15/92 vs PHEN/TPM 7.5/46			1.7 (0.53)	0.0683			2.2 (0.62)	0.0050			1.7 (0.44)	0.0552
Source: Applicant's Post-text Table 14.2.5, 14.2.6, Pg 105, 116, OB-305 CSR Odds ratio, SE, 95% CI, and two-sided p-value are obtained from a logistic regression model with treatment, gender, and diabetic status as fixed effects, and baseline weight as a covariate												

Weight loss/gain in second year

Figure 2 shows the mean percent weight loss over time by treatment group for the Modified ITT Set. The graphical presentation of weight loss data for the Modified ITT Set includes only weight measurements for subjects obtained while on study drug or within 7 days of the last dose of study drug.

Figure 2: Percent weight loss over two-year period - MITT



Source: Study OB-305 Pg 71 CSR

The applicant submitted analyses that assessed the weight lost or gained in the second year as a median percentage of the weight lost in the first year of treatment. The results of the analyses demonstrated that in the placebo group, 26.8% of weight lost in the first year was regained, 10.9% of weight lost in the first year was regained in the mid-dose PHEN/TPM group, and 18.4% of weight lost in the first year was regained in the high-dose PHEN/TPM group (Table 12). The difference in median percent weight change between the mid- and high-dose PHEN/TPM groups was statistically significant ($p=0.03$), whereas the differences in median percent weight change between mid- and high-dose PHEN/TPM groups and placebo were not.

Table 12: Percent weight change from Week 56 to Week 108 with LOCF relative to weight lost from baseline to Week 56 and treatment comparisons (ITT set)

Treatment	n [1,2]	Baseline to Week 56 [2] Mean (SD)	Week 56 to Week 108 With LOCF [3] Mean (SD)	Percent Weight Change [4,5] From Week 56 to Week 108 With LOCF[3]		
				Mean (SD)	Median (IQR)	P-value
Placebo	165	-6.0 (6.39)	1.4 (4.34)	4.3 (590.74)	26.8 (122.11)	0.0019
PHEN/TPM 7.5/46	142	-12.6 (7.57)	1.2 (4.63)	11.3 (101.66)	10.9 (37.07)	0.0011
PHEN/TPM 15/92	273	-15.1 (8.25)	2.6 (4.68)	24.1 (73.00)	18.4 (33.42)	<0.0001
Treatment Comparison				Difference (Tmt 1 – Tmt 2) [6]		
				Median (IQR)	95% CI	P-value
PHEN/TPM 15/92 (Tmt 1) vs. Placebo (Tmt 2)				-7.7 (136.87)	(-20.1 , 4.43)	0.9204
PHEN/TPM 7.5/46 (Tmt 1) vs. Placebo (Tmt 2)				-16.8 (146.46)	(-32.1 , -1.92)	0.1034
PHEN/TPM 15/92 (Tmt 1) vs. PHEN/TPM 7.5/46 (Tmt 2)				7.6 (69.96)	(0.5 , 15.0)	0.0271

1. n is the number of subjects experiencing weight loss from baseline to Week 56 and having values at both time points.
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303.
3. Week 108 with LOCF is the last available weight measurement during the double-blind treatment period in study OB-305.
4. Percent weight change is: $100 \times (\text{weight at time point} - \text{weight at Week 56}) / (\text{baseline weight} - \text{weight at Week 56})$.
5. Median estimate of the within-treatment percent change is obtained using the Hodges-Lehmann estimator and the p-value testing for a significant change over the treatment period is obtained from the Wilcoxon signed-rank test.
6. Median estimate of the treatment difference is obtained using the Hodges-Lehmann estimator, the 95% confidence interval is estimated using the method of Moses, and the p-value is obtained from a rank analysis of covariance weight loss during OB-303 as a covariate.
CI = confidence interval; IQR = interquartile range; LOCF = last observation carried forward; PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SD = standard deviation; Tmt = treatment; vs. = versus.
Source: [Post-text Table 14.2.118](#)

In another assessment of weight regain in the second year of treatment, the applicant submitted the percentage of subjects with no weight regain or weight regain of $\leq 5\%$, $\leq 10\%$, $\leq 15\%$, $\leq 20\%$ relative to weight loss in the first year of treatment (Table 13). The mid-dose PHEN/TPM group had the highest numerical proportion of subjects who did not gain weight at all or by varying degrees during the second year of treatment relative to weight lost in the first year. The high-dose group had the lowest percentage of subjects that maintained weight loss. These numerical differences were not statistically significant between PHEN/TPM and placebo groups or between mid-dose and high-dose PHEN/TPM groups.

Table 13: Study OB-305: Number (%) of subjects with no weight gain and $\leq 5\%$ weight gain in second year (Week 56 to Week 108 LOCF) relative to first year weight loss (Baseline to Week 56) – ITT

	n (%)	p-value vs. placebo	p-value high vs mid-dose PHEN/TPM
No weight gain			
Placebo N=165 [1]	60 (36.4)	--	
PHEN/TPM 7.5/46 N=142	53 (37.3)	0.19	--
PHEN/TPM 15/92 N=273	77 (28.2)	0.92	0.11
$\leq 5\%$ Weight gain			
Placebo N=165 [1]	62 (37.6)	--	--
PHEN/TPM 7.5/46 N=142	62 (43.7)	0.10	--
PHEN/TPM 15/92	95 (34.8)	0.79	0.18

	n (%)	p-value vs. placebo	p-value high vs mid-dose PHEN/TPM
N=273			
Source: Applicant's Table 15, OB-305 CSR, Pg 69 Week 56 is the last available weight measurement on or before the first dose of double-blind study drug in study OB-305. Week 108 with LOCF is the last available weight measurement during the double-blind treatment period in study OB-305. Percent weight change is: $100 \times (\text{weight at time point} - \text{weight at Week 56}) / (\text{baseline weight} - \text{weight at Week 56})$. Two-sided p-value are from a logistic regression model with treatment, gender, and diabetic status as fixed effects and (baseline weight – weight at Week 56) as a covariate.			

Another way to assess weight regain was undertaken by the FDA statistical reviewer. In an analysis of individuals actively taken study drug, the mean percent weight change from Week 56 to Week 108 was greatest in the high-dose PHEN/TPM group. The placebo-treated group had the least amount of weight gain from Week 56 to Week 108. Please see further details of this analysis in the full FDA statistical review included in this briefing package.

Waist circumference

In all Phase 3 studies, waist circumference decreased significantly in PHEN/TPM-treated subjects compared to placebo-treated subjects in a dose-related manner (Table 14).

In study OB-303, there was a statistically significant treatment difference between mid- and high-dose PHEN/TPM treatment groups at Week 56.

In the subjects treated in OB-305, there was no statistical difference between mid- and high-dose PHEN/TPM groups at Week 108.

Table 14: Change in waist circumference at Week 56 and Week 108 (LOCF) – ITT set

Waist circumference (cm)			
Study	Treatment group	LS mean (SE) change from baseline	p-value [3]
OB-302 [1] Week 56	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] Week 56	Placebo	-2.4 (0.30)	--
	PHEN/TPM 7.5/46	-7.6 (0.40)	<0.0001
	PHEN/TPM 15/92	-9.2 (0.30)	<0.0001
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	-1.5 (0.44)	0.0004
OB-305 Week 108	Treatment group	LS mean (SE) change from baseline	p-value [3]
	Placebo	-3.6 (0.55)	--
	PHEN/TPM 7.5/46	-9.8 (0.68)	<0.0001
	PHEN/TPM 15/92	-10.6 (0.50)	<0.0001
		LS mean (SE) dose difference	p-value [4]

Waist circumference (cm)			
Study	Treatment group	LS mean (SE) change from baseline	p-value [3]
		difference	
	High vs Mid PHEN/TPM	-0.78 (0.77)	0.3108
[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 PHEN/TPM with placebo or high versus mid-dose PHEN/TPM [4] Two-sided p-value is for treatment comparison of high-dose minus mid-dose PHEN/TPM Source: Applicant's Table 15, Pg 66; ISE			

Blood pressure

In studies OB-302 and OB-303, at Week 56, SBP decreased significantly in PHEN/TPM-treated subjects compared to placebo at all dose levels (Table 15). PHEN/TPM treatment at low- and mid-doses did not obtain statistically significant decreases in DBP over placebo; however, high-dose PHEN/TPM treatment did. In a subgroup of hypertensive subjects in study OB-303, mid- and high-dose PHEN/TPM treatment was associated with a significant reduction in blood pressure compared to placebo treatment.

In study OB-305, there were no statistically significant differences in blood pressure between PHEN/TPM treatment groups and placebo overall. In a subgroup of subjects with hypertension at baseline there was no statistically significant treatment differences in blood pressure between PHEN/TPM and placebo groups, however, the PHEN/TPM treatment group had a numerically larger reduction in systolic blood pressure compared to the placebo treatment group at Week 108. The change in number of concomitant anti-hypertensive medications was more favorable and statistically significant in the PHEN/TPM-treated subjects compared to placebo-treated subjects (p=0.02) (Table 16).

Table 15: Changes in systolic and diastolic blood pressure at Week 56 and 108 (LOCF) – ITT set

Blood pressure (mmHg)					
Study	Treatment group	Systolic blood pressure		Diastolic blood pressure	
		LS mean (SE) from baseline	p-value [4]	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
		LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]
	High vs Mid PHEN/TPM	-0.8 (0.69)	0.2217	-0.4 (0.46)	0.3720

Blood pressure (mmHg)					
		Systolic blood pressure		Diastolic blood pressure	
Study	Treatment group	LS mean (SE) from baseline	p-value [4]	LS mean (SE) from baseline	p-value [4]
OB-303 (Hypertension subgroup [3])	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
		LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]
	High vs Mid PHEN/TPM	-2.2 (1.02)	0.0328	-0.6 (0.67)	0.3568
OB-305 [2]	Placebo	-3.2 (0.85)	--	-3.9 (0.58)	--
	PHEN/TPM 7.5/46	-4.7 (1.05)	0.2441	-3.7 (0.71)	0.8830
	PHEN/TPM 15/92	-4.3 (0.78)	0.3177	-3.5 (0.53)	0.5815
		LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]
	High vs Mid PHEN/TPM	0.4 (1.19)	0.7342	0.3 (0.81)	0.7389
OB-305 (Hypertension subgroup[3])	Placebo	-6.7 (1.18)	--	-5.7 (0.76)	--
	PHEN/TPM 7.5/46	-6.9 (1.53)	0.9274	-4.8 (0.99)	0.4693
	PHEN/TPM 15/92	-8.6 (1.04)	0.2327	-5.8 (0.67)	0.8872
		LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]
	High vs Mid PHEN/TPM	-1.7 (1.85)	0.3571	-1.0 (1.2)	0.3813
<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] Subjects 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</p> <p>[4] Two-sided p-value is for treatment comparison of PHEN/TPM with placebo or high versus mid-dose PHEN/TPM.</p> <p>[5] Two-sided p-value is for treatment comparison of high versus mid-dose PHEN/TPM</p> <p>Source: Applicant's Table 16-17, 42-43 OB-305 CSR, Pg 72-73, 95-96; Applicant's Table 16, Pg 68 ISE</p>					

Table 16: Changes in concomitant antihypertensive medications – OB-303/305 safety set

	Number (%) of subjects		
	Decrease n (%)	No change n (%)	Increase n (%)
Placebo N=227	17 (7.5)	185 (81.5)	25 (11.0)
PHEN/TPM 7.5/46 N=153	20 (13.1)	119 (77.8)	14 (9.2)
PHEN/TPM 15/92 N=295	46 (15.6)	232 (78.6)	17 (5.8)
Source: Applicant's Table 18, OB-305 CSR, Pg 73			

Lipid parameters

Overall, improvements in lipid parameters with PHEN/TPM were generally small with varying degrees of nominal statistical significance compared to placebo (Table 17). While LDL-C decreased in a statistically significant manner with high-dose PHEN/TPM treatment compared to placebo in the 1-year studies (OB-302, OB-303), in study OB-305 PHEN/TPM treatment (-4.6% mid-dose, -5.6% high-dose) did not demonstrate a greater reduction in LDL-C compared to placebo (-10.7%).

PHEN/TPM treatment showed a consistent pattern of favorable changes in HDL-C and triglyceride values compared to placebo treatment in the 1-year studies (OB-302, OB-303) and the study OB-305.

There were no significant treatment differences between mid- and high-dose PHEN/TPM groups except in HDL-C (p=0.02) favoring high-dose PHEN/TPM in study OB-305.

The change in number of concomitant anti-dyslipidemic medications was more favorable and statistically significant in the PHEN/TPM-treated subjects compared to placebo-treated subjects (p=0.01) (Table 18) in study OB-305. There was no specified protocol for managing lipids in the clinical development program.

Table 17: Percent changes in lipid parameters at Week 56 and Week 108 (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] Week 56	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] Week 56	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
		LS mean	p-value	LS mean	p-value [5]	LS mean	p-value	LS mean	p-value

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]
		(SE) dose difference	[5]	(SE) dose difference		(SE) dose difference	[5]	(SE) dose difference	[5]
	High vs Mid PHEN/TPM	-3.2 (1.26)	0.0110	1.6 (0.95)	0.0986	-1.4 (0.77)	0.0756	-2.0 (2.45)	0.4072
OB-303 [3] High TG subgroup [6] Week 56	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
		LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]
	High vs Mid PHEN/TPM	-4.9 (2.32)	0.0336	1.1 (1.76)	0.5280	-2.1 (1.27)	0.1008	-1.4 (3.35)	0.6653
OB-305 [2] Week 108	Placebo	-10.7 (1.54)	--	4.7 (1.37)	--	-7.0 (0.99)	--	0.4 (2.66)	--
	PHEN/TPM 7.5/46	-4.6 (1.89)	0.0066	7.3 (1.68)	0.2100	-5.8 (1.22)	0.4306	-12.5 (3.26)	0.0010
	PHEN/TPM 15/92	-5.6 (1.40)	0.0077	11.9 (1.25)	<0.0001	-5.2 (0.91)	0.1512	-13.7 (2.42)	<0.0001
		LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]
	High vs Mid PHEN/TPM	-1.1 (2.1)	0.6203	4.6 (1.9)	0.0154	0.6 (1.4)	0.6577	-1.2 (3.7)	0.7562
OB-305[3] High TG subgroup [6] Week 108	Placebo	-10.9 (2.53)	--	9.1 (2.34)	--	-8.4 (1.53)	--	-14.3 (3.69)	--
	PHEN/TPM 7.5/46	7.7 (3.27)	<0.0001	11.4 (3.01)	0.5316	-2.5 (1.98)	0.0189	-25.9 (4.77)	0.0547
	PHEN/TPM 15/92	-2.8 (2.21)	0.0167	16.7 (2.04)	0.0150	-6.2 (1.34)	0.2785	-26.3 (3.22)	0.0150

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]
		LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]	LS mean (SE) dose difference	p-value [5]
	High vs Mid PHEN/TPM	-10.5 (3.94)	0.0081	5.2 (3.65)	0.1520	-3.7 (2.39)	0.1212	-0.4 (5.76)	0.9497
<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 PHEN/TPM minus placebo</p> <p>[5] Two-sided p-value is for treatment comparison of high-dose minus mid-dose PHEN/TPM</p> <p>[6] Subjects defined at baseline with TG \geq200 mg/dL and \leq400 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 Applicant's Table 19-22, OB-305 CSR, Pg 74-77</p>									

Table 18: Change in concomitant lipid-lowering medications from baseline to end of study – OB 305 safety set

	Number (%) of subjects		
	Decrease n (%)	No change n (%)	Increase n (%)
Placebo N=227	7 (3.1)	174 (76.7)	46 (20.3)
PHEN/TPM 7.5/46 N=153	9 (5.9)	127 (83.0)	17 (11.1)
PHEN/TPM 15/92 N=295	17 (5.8)	247 (83.7)	31 (10.5)
<p>Source: Applicant's Table 23, OB-305 CSR, Pg 77</p> <p>Includes data from OB-303 and OB-305</p> <p>Baseline defined as the last measurement obtained on or before the first dose date of double-blind study medication in study OB-303</p>			

Hemoglobin A1c and fasting serum glucose

Changes in HbA1c for studies OB-303 and OB-305 are presented in the table below. Study OB-302 did not assess the change in HbA1c. Treatment with PHEN/TPM in both studies resulted in statistically significant reductions in HbA1c compared to treatment with placebo.

In the diabetic subgroup of study OB-303 there was a 0.3 percentage point reduction in HbA1c with PHEN/TPM treatment over placebo ($p < 0.05$). In study OB-305's diabetic subgroup, there were no statistical significant treatment differences between the PHEN/TPM and placebo groups at Week 108, even though PHEN/TPM-treated diabetics experienced a numerically larger reduction in HbA1c compared to placebo-treated diabetics.

Table 19: Change in Hemoglobin A1c at Week 56 and Week 108 (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
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	-0.0 (0.02)	0.3306
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
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	-0.0 (0.12)	0.9795
Study	Treatment group	Change at Week 108 (LOCF)	
		LS mean (SE) from Baseline (%)	p-value [3]
OB-305 [1]	Placebo	0.2 (0.04)	--
	PHEN/TPM 7.5/46	0.0 (0.05)	0.0042
	PHEN/TPM 15/92	0.0 (0.04)	0.0003
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	-0.01 (0.05)	0.8564
OB-305 [2] (Diabetic subgroup)	Placebo n=55	-0.0 (0.13)	--
	PHEN/TPM 7.5/46 n=26	-0.4 (0.19)	0.1056
	PHEN/TPM 15/92 n=64	-0.2 (0.12)	0.2739
		LS mean (SE) dose difference	p-value [4]

HbA1c (%)			
Study	Treatment group	Change at Week 56 (LOCF)	
		LS mean (SE) from Baseline (%)	p-value [3]
		difference	
	High vs Mid PHEN/TPM	0.2 (0.23)	0.4231
[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; Applicant's Table 22, 39 Pg 77, 92; OB-305 CSR			

Mid- and high-dose PHEN/TPM treatment resulted in a nominally significant decrease in fasting glucose compared to placebo in the 1-year studies (OB-302 and OB-303).

Only high-dose PHEN/TPM treatment resulted in a nominally significant decrease in fasting glucose compared to placebo at Week 108 in study OB-305.

No statistical differences in fasting glucose were noted between PHEN/TPM-exposed and placebo-exposed subjects with diabetes in the long-term extension cohort, although the changes were numerically more favorable in the PHEN/TPM exposed group. In addition, the percentage of subjects with an increase in the number of concomitant antidiabetic medications from baseline to the end of the study was higher in the placebo group than in the PHEN/TPM groups. The percentage of subjects with a decrease in the number of concomitant antidiabetic medications was higher in the high-dose PHEN/TPM group than in the placebo group (Table 21).

Table 20: Change in fasting serum glucose at Week 56 and Week 108 (LOCF) – ITT set

Fasting Serum Glucose (mg/dL)			
Study	Treatment group	LS mean (SE) change from Baseline (mg/dl)	p-value [3]
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
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	-1.2 (0.85)	0.1634
OB-303 (Diabetic subgroup) [1]	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
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	-2.2 (4.26)	0.6089

Fasting Serum Glucose (mg/dL)			
Study	Treatment group	LS mean (SE) change from Baseline (mg/dl)	p-value [3]
OB-305 [2]	Placebo	3.7 (1.45)	--
	PHEN/TPM 7.5/46	0.1 (1.80)	0.0872
	PHEN/TPM 15/92	-1.2 (1.33)	0.0048
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	-1.4 (1.96)	0.4860
OB-305 (Diabetic subgroup) [2]	Placebo (n =55)	-6.3 (5.03)	--
	PHEN/TPM 7.5/46 (n=26)	-10.6 (7.38)	0.6256
	PHEN/TPM 15/92 (n=64)	-7.4 (4.70)	0.8649
		LS mean (SE) dose difference	p-value [4]
	High vs Mid PHEN/TPM	3.2 (8.77)	0.7148
[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 PHEN/TPM with placebo. [4] Two-sided p-value is for treatment comparison of high-dose minus mid-dose PHEN/TPM Source: Applicant's Table 41, 43, Pg 104, 107; ISE			

Table 21: Change in concomitant antidiabetic medications – OB-305 safety set

	Number (%) of subjects		
	Decrease n (%)	No change n (%)	Increase n (%)
Placebo N=227	3 (1.3)	205 (90.3)	19 (8.4)
PHEN/TPM 7.5/46 N=153	1 (0.7)	148 (96.7)	4 (2.6)
PHEN/TPM 15/92 N=295	9 (3.1)	277 (93.9)	9 (3.1)
Source: Applicant's Table 27, OB-305 CSR, Pg 80 Includes data from OB-303 and OB-305 Baseline defined as the last measurement obtained on or before the first dose date of double-blind study medication in study OB-303			

Onset of type 2 diabetes

The following table presents the annualized incidence rate of type 2 diabetes across the 2-year study period based on consecutive measurements of a fasting glucose ≥ 126 mg/dL or 2-hour OGTT glucose ≥ 200 mg/dL in subjects without type 2 diabetes at entry into study OB-303 (Table 22). The incidence of new onset type 2 diabetes was 7.0% in the placebo group compared to 3.2% in the mid-dose PHEN/TPM group and 1.7% in the high-dose PHEN/TPM group.

Table 22: Annualized incidence rate of type 2 diabetes in subjects without type 2 diabetes at time of study entry into study OB-303 – ITT set

	Placebo (N=171)	PHEN/TPM 7.5/46 (N=125)	PHEN/TPM 15/92 (N=229)
n (%) [1]	12 (7.0)	4 (3.2)	4 (1.7)
Subject-years of follow up [2]	326.6	242.4	455.5
Annualized incidence rate [3]	3.7	1.7	0.9
Relative Risk [4]			
Estimate		0.46	0.25
95% CI		(0.15 , 1.38)	(0.08 , 0.76)
<p>Note: Five subjects did not have diabetes at the time of entry into study OB-303 but did have onset on or before the first dose date of study drug in study OB-303 and have been excluded from this analysis.</p> <ol style="list-style-type: none"> n is the number of subjects newly diagnosed with type 2 diabetes based on consecutive measurements of fasting glucose ≥ 126 mg/dL or OGTT glucose ≥ 200 mg/dL. Subject-years of follow up is calculated as the sum across all subjects of the number of days from the randomization date in study OB-303 to the date of onset of type 2 diabetes (or censoring time if the subject did not develop type 2 diabetes) divided by 365.25. The date of onset is the date of the first occurrence of consecutive post-baseline measurements of fasting glucose ≥ 126 mg/dL or OGTT glucose ≥ 200 mg/dL. Censoring time is calculated as the number of days from the randomization date in study OB-303 to the completion or early termination date from study OB-305. Annualized incidence rate per 100 subjects years is calculated as $100 \times \text{number of newly diagnosed subjects} / \text{subject-years of follow up}$. Relative risk was calculated as PHEN/TPM vs. placebo. <p>CI = confidence interval; OGTT = oral glucose tolerance testing; PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate.</p> <p>Source: Post-text Table 14.2.107</p>			

Subgroups Analyses

The table below presents the LS mean percent weight loss and between-treatment comparisons at Week 56 with LOCF (OB-303) and Week 108 with LOCF (OB-305) for various subgroups.

The treatment effect of PHEN/TPM on percent weight loss was numerically larger for women; non-blacks; people younger than 65 years old, subjects with higher baseline BMI, and non-diabetics in both studies.

Table 23: Subgroup analyses LS mean percent weight loss from baseline and between treatment comparisons Week 56 LOCF and Week 108 LOCF - ITT set

	OB-303 (Week 56 LOCF)						OB-305 (Week 108 LOCF)					
	LS mean (SE) % wt loss from baseline			LS mean (SE) % treatment difference			LS mean (SE) % wt loss from baseline			LS mean (SE) % treatment difference		
	Placebo	PHEN/TPM 7.5/46	PHEN/TPM 15/92	PHEN/TPM 7.5/46 vs Placebo	PHEN/TPM 15/92 vs Placebo	PHEN/TPM 15/92 vs PHEN/TPM 7.5/46	Placebo	PHEN/TPM 7.5/46	PHEN/TPM 15/92	PHEN/TPM 7.5/46 vs Placebo	PHEN/TPM 15/92 vs Placebo	PHEN/TPM 15/92 vs PHEN/TPM 7.5/46
Male	2.2 (0.39)	7.5 (0.55)	9.1 (0.39)	5.3 (0.68)	6.9 (0.55)	1.6 (0.67)	2.5 (0.72)	8.3(0.94)	9.8 (0.64)	5.8 (1.18)	7.3 (0.96)	1.6 (1.13)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0156	0.0006	<0.0001	<0.0001	<0.0001	<0.0001	0.1741
Female	1.6 (0.29)	8.8 (0.41)	11.0 (0.29)	7.2 (0.50)	9.4 (0.40)	2.2 (0.50)	2.6 (0.67)	11.2 (0.79)	12.2 (0.59)	8.5 (1.04)	9.5 (0.89)	1.0 (0.99)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.2994
Black	0.5 (0.64)	7.3 (0.95)	9.7 (0.62)	6.7 (1.15)	9.1 (0.89)	2.4 (1.13)	1.4 (1.46)	6.9 (1.9)	10.7 (1.17)	5.5 (2.40)	9.4 (1.87)	3.9 (2.25)
	0.3991	<0.0001	<0.0001	<0.0001	<0.0001	0.0325	0.3576	0.0005	<0.0001	0.0235	<0.0001	0.0898
Non-Black	2.0 (0.25)	8.5 (0.35)	10.5 (0.25)	6.6 (0.43)	8.5 (0.35)	2.0 (0.43)	2.7 (0.55)	10.7 (0.66)	11.5 (0.49)	8.0 (0.86)	8.8 (0.73)	0.8 (0.82)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.3314
< 65 years	1.7 (0.24)	8.5 (0.35)	10.5 (0.25)	6.8 (0.42)	8.8 (0.35)	2.0 (0.43)	2.4 (0.54)	10.6 (0.66)	11.4 (0.48)	8.2 (0.86)	9.0 (0.72)	0.76 (0.82)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.3508
≥ 65 years	3.2 (0.79)	7.8 (1.06)	9.4 (0.75)	4.7 (1.32)	6.3 (1.09)	1.6 (1.29)	4.3 (1.58)	8.1 (1.86)	11.4 (1.36)	3.7 (2.44)	7.1 (2.09)	3.4 (2.30)
	<0.0001	<0.0001	<0.0001	0.0005	<0.0001	0.2132	0.0079	<0.0001	<0.0001	0.1332	0.0012	0.1492
<30 kg/m²	1.1 (0.75)	9.1 (1.08)	9.2 (0.76)	8.0 (1.33)	8.1 (1.07)	0.14 (1.34)	1.2 (1.15)	8.3 (1.64)	6.9 (1.07)	7.1 (2.01)	5.7 (1.57)	-1.4 (1.95)
	0.1520	<0.0001	<0.0001	<0.0001	<0.0001	0.9139	0.2951	<0.0001	<0.0001	0.0008	0.0006	0.4651
≥ 30-35 kg/m²	ND	ND	ND	ND	ND	ND	1.5 (0.96)	11.2 (1.01)	10.5 (0.84)	9.7 (1.39)	9.0 (1.27)	-0.67 (1.31)
	ND	ND	ND	ND	ND	ND	0.1318	<0.0001	<0.0001	<0.0001	<0.0001	0.6103
≥ 35 kg/m²	2.0 (0.30)	8.6 (0.44)	10.6 (0.30)	6.7 (0.54)	8.6 (0.4)	2.0 (0.54)	3.4 (0.68)	10.1 (0.88)	12.6 (0.59)	6.8 (1.12)	9.3 (0.90)	2.5 (1.1)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0193
DM	1.9 (0.57)	6.8 (0.87)	8.8 (0.56)	4.9 (1.04)	6.9 (0.80)	2.0 (1.04)	2.0 (1.06)	9.0 (1.55)	9.0 (0.98)	7.0 (1.87)	7.0 (1.84)	0.0 (1.84)
	0.0008	<0.0001	<0.0001	<0.0001	<0.0001	0.0598	0.0590	<0.0001	<0.0001	0.0003	<0.0001	0.9990
No DM	1.8 (0.26)	8.7 (0.36)	10.7 (0.26)	6.9 (0.44)	8.9 (0.36)	2.1 (0.44)	2.7 (0.59)	10.7 (0.68)	12.0 (0.50)	7.9 (0.90)	9.3 (0.77)	1.3 (0.85)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.1131

Source: Post-text Table 14.2.87, 90, 93, 99, 102, 105, 108, 111, 137, 140 OB-303 CSR Post-text Table 14.2.58,61, 65, 68, 71, 73, 77, 79, 82, 83, 85, 88 OB-305 CSR

Highlights of PHEN/TPM Efficacy

- In the 1-year studies, OB-302 and OB-303, treatment with low-, mid-, and high-dose PHEN/TPM was associated with a higher proportion of subjects losing 5% or greater of body weight compared to placebo. Mid- and high-dose PHEN/TPM treatment resulted in LS mean percent placebo-subtracted weight loss of > 5%.
- From the ITT LOCF analyses of study OB-305, the 1-year extension of eligible subjects from study OB-303, subjects treated with mid- and high-dose PHEN/TPM had an LS mean percent weight loss from baseline of 9.3% and 10.5%, respectively, after two years of treatment, compared with a LS mean percent weight loss of 1.8% for subjects treated with placebo. The proportion of subjects achieving $\geq 5\%$ weight loss with PHEN/TPM was more than double that with placebo (75% and 79% with mid-dose and high-dose PHEN/TPM, respectively, versus 30% with placebo).
- All treatment groups in study OB-305 gained weight in the second year of treatment.
- An assessment of weight lost or gained in the second year as a median percentage of the weight lost in the first year of treatment demonstrated that subjects on placebo regained a greater proportion of the weight lost during the first year (median percent weight change 26.8%) followed by high-dose PHEN/TPM-treated subjects (median percent weight change 18.4%), and mid-dose PHEN/TPM-treated subjects (median percent weight change 10.9%).
- Of subjects who lost weight in the first year, mid-dose PHEN/TPM-treated subjects had the highest numerical proportion of subjects with no weight gain during the second year of treatment relative to the weight lost in the first year and high-dose PHEN/TPM-treated subjects had the lowest percentage of subjects with no weight gain even when compared to placebo-treated subjects.
- Subjects treated with PHEN/TPM had a LS mean reduction in waist circumference of approximately 2.5 cm (low-dose) and 7.8 cm (high-dose) over placebo at 1-year (OB-302, Week 56 LOCF) and approximately 6.2 cm (mid-dose) and 7.0 cm (high-dose) over placebo at two years (OB-305 Week 108 LOCF).
- Overall, greater reductions in systolic blood pressure were observed in subjects treated with PHEN/TPM versus placebo. The 1-year studies (OB-302, OB-303) noted a statistically significant treatment difference with PHEN/TPM over placebo in systolic blood pressure of approximately 2 to 4 mmHg. In study OB-305, at Week 108, there were no statistically significant treatment differences for systolic or diastolic blood pressure with PHEN/TPM over placebo.
- Improvements in lipid parameters were modest and generally favorable with PHEN/TPM treatment in the 1-year studies and 2-year study.
- In study OB-303, there was a LS mean difference of -0.1% in HbA1c with high-dose PHEN/TPM compared to placebo at Week 56. In study OB-305 at Week 108, HbA1c did not change with PHEN/TPM treatment but individuals treated with placebo had an increase in HbA1c of 0.2%. In a subset of overweight or obese subjects with type 2 diabetes at baseline, high-dose PHEN/TPM treatment reduced HbA1c by 0.3% compared to placebo treatment in study OB-303. Mid and high-dose PHEN/TPM treatment reduced HbA1c by 0.4% to 0.2% compared to placebo treatment in a subgroup of subjects with type 2 diabetes in study OB-305.
- In study OB-305, the incidence of new onset diabetes defined as consecutive measurements of a fasting glucose ≥ 126 mg/dL or 2-hour OGTT glucose ≥ 200 mg/dL was 7.0% in the

placebo group compared to 3.2% in the mid-dose PHEN/TPM group and 1.7% in the high-dose PHEN/TPM group. The relative risk reduction versus placebo was statistically significant only for the high-dose group.

Conclusions regarding PHEN/TPM efficacy

Treatment with PHEN/TPM demonstrated clinically and statistically significant weight loss compared to placebo after 1 year of treatment and depending on dose, met one or both of the Division's benchmarks for weight-loss efficacy. The data from an enriched subgroup from study OB-303 evaluated over two years was supportive of the 1 year findings. During the 2-year study period, weight regain was observed in PHEN/TPM-treated subjects after 18 to 21 months of treatment. Of subjects who lost weight during the first year of treatment, subjects treated with placebo regained a greater proportion of the weight loss in the first year of treatment. Mid-dose PHEN/TPM treated subjects were more successful in maintaining weight loss than placebo or high-dose PHEN/TPM-treated subjects. Favorable changes in weight-related co-morbidities such as waist circumference, blood pressure, lipid parameters, and glycemic control were observed with PHEN/TPM treatment.

IV. Integrated Summary of Safety

This section will primarily focus on new information from OB-305, the 1-year extension study, of selected sites with eligible subjects from OB-303. Comparisons may be made to the 1-year safety cohort submitted with the original NDA. These two safety cohorts are defined below.

Safety cohorts

- **One-year safety cohort:** This cohort comprises all randomized subjects from studies OB-302 and OB-303 and all subjects who entered study DM-230, the 6-month extension to study OB-202. Data for subjects in OB-202 and DM-230 were combined to provide 1-year safety data. Study OB-202/DM-230 was a randomized, double-blind, placebo-controlled study of overweight and obese adults with type 2 diabetes.
- **Two-year safety cohort:** This cohort consists of all eligible subjects from selected sites from study OB-303 who entered study OB-305, the 1-year extension study to OB-303. Data are presented for these subjects that summarizes the two-year treatment period (OB-303 and OB-305).

Exposure to study drug

The overall extent of exposure to study drug in the 2-year cohort before adjustment for drug holidays or dose modification was a mean of 728.5 days and median of 756 days. In total 318 subjects (47.1%) in the 2-year cohort had 108 to 112 weeks exposure. Exposure to study drug adjusting for drug holidays was similar to unadjusted.

Table 24: Extent of exposure to study drug – 2-year cohort (safety set)

Extent of exposure to study drug – 2-year cohort (safety set)				
2-year cohort				
	Placebo N=227	PHEN/TPM 7.5/46 N=153	PHEN/TPM 15/92 N=295	Total N=675
Mean (SD), days	733.4 (75.22)	724.4 (92.31)	726.9 (85.88)	728.5 (83.96)
Median, days	757.0	757.0	756.0	756.0
>104 weeks to ≤108 weeks, n (%)	82 (36.1)	49 (32.0)	115 (39.0)	246 (36.4)
>108 weeks to ≤112 weeks, n (%)	113 (49.8)	78 (51.0)	127 (43.1)	318 (47.1)
Applicant's Tables 48, Pg 104, OB-305 CSR				

Dose modifications

The following table presents the number and frequency of dosing modifications for subjects over the 2-year study period. A higher percentage of subjects on PHEN/TPM had a change in study medication dosing compared to the placebo group. A greater proportion of subjects treated with high-dose PHEN/TPM had a drug holiday, drug reduction, or switch to every other day dosing compared to subjects treated with mid-dose PHEN/TPM or placebo. Within the second year of

treatment there were no dose reductions and the majority of changes were drug holidays. Overall, the majority (148 of 178) of subjects with any change in their dosing regimen completed the study on study drug.

Table 25: Summary of changes to study medication – 2-year cohort (safety set)

2-year cohort (Safety set)				
	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Any change to study medication dosing	49 (21.6)	41 (26.8)	88 (29.8)	129 (28.8)
Drug holiday	38 (16.7)	29 (19.0)	60 (20.3)	89 (19.9)
Drug Tolerability	2 (0.9)	6 (3.9)	18 (6.1)	24 (5.4)
Event not related to drug	11 (4.8)	10 (6.5)	16 (5.4)	26 (5.8)
Other	25 (11.0)	15 (9.8)	36 (12.2)	51 (11.4)
Drug reduction	7 (3.1)	15 (9.8)	46 (15.6)	61 (13.6)
Drug tolerability	4 (1.8)	10 (6.5)	32 (10.8)	42 (9.4)
Event not related to drug	0	0	2 (0.7)	2 (0.4)
Other	3 (1.3)	5 (3.3)	14 (4.7)	19 (4.2)
Uptitration after dose reduction	0	7 (4.6)	16 (5.4)	23 (5.1)
Switch to QOD dosing	6 (2.6)	14 (9.2)	40 (13.6)	34 (7.6)
Drug tolerability	3 (1.3)	7 (4.6)	24 (8.1)	31 (6.9)
Event not related to drug	1 (0.4)	0	6 (2.0)	6 (1.3)
Other	2 (0.9)	4 (2.6)	12 (4.1)	16 (3.6)
Return to daily dosing after switch to QOD dosing	4 (1.8)	13 (8.5)	36 (12.2)	49 (10.9)
Includes data from studies OB-303/305 Source: OB-305 CSR Table 14.1.3				

Drug holidays

In the 2-year safety cohort, a higher proportion of PHEN/TPM-treated subjects required at least one drug holiday (16.7% placebo, 19% mid-dose PHEN/TPM, 20.3% high-dose PHEN/TPM) and had a total holiday duration of greater than 1 month (1.3% placebo, 4.6% mid-dose PHEN/TPM, 4.7% high-dose PHEN/TPM) compared to placebo-treated subjects. The average holiday duration was slighter higher in PHEN/TPM-exposed subjects compared to placebo-exposed subjects (17.9 days placebo, 26.1 days mid-dose PHEN/TPM, 23.3 days high-dose PHEN/TPM). In the 2-year safety cohort, the majority (106 of 127) of subjects who required a drug holiday completed the study on drug.

Table 26: Summary of drug holidays – 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Number (%) of subjects requiring:			
• No holiday	189 (83.3)	124 (81.0)	235 (79.7)
• At least one holiday	38 (16.7)	29 (19.0)	60 (20.3)
○ One holiday	29 (12.8)	24 (15.7)	43 (14.6)
○ Two holidays	8 (3.5)	3 (2.0)	11 (3.7)
○ Three holidays	1 (0.4)	2 (1.3)	4 (1.4)
○ Four or more holidays	0	0	2 (0.7)
Number (%) of subjects with total holiday duration > 1 month	3 (1.3)	7 (4.6)	14 (4.7)
Drug holiday duration days			
• Mean (SD)	17.9 (22.86)	26.1 (23.61)	23.3 (38.62)
• Median	10.5	18.0	10.0
Source: Applicant's Table 25, Pg 88, ISE			

Adverse Events

Definition of adverse events

Adverse events (AEs) were defined as any untoward medical occurrence in subjects 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 subjects 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.

Overall adverse events

Table 27 presents the overall adverse events. Over 90% of subjects experienced a treatment-emergent adverse event (TEAE) during the 2-year study period. There were no deaths. There were 47 (7.1%) subjects experiencing a non-fatal treatment emergent serious adverse event

(SAE) within the 2-year study period. The majority occurred in the high-dose PHEN/TPM-treated group (8.1%) versus the placebo-treated group (6.2%). In order to participate in the second year of treatment one had to be on drug at the end of the first year; therefore, all of the study drug discontinuations occurred in the second year of treatment. In total, 27 (4.0%) subjects discontinued study drug in the second year of treatment due to either an adverse event that began in the first or second year. There were a higher proportion of PHEN/TPM-treated subjects (4.5%) who discontinued study drug treatment due to an adverse event compared to placebo-treated subjects (3.1%).

Table 27: Overview of adverse events – 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Treatment-emergent adverse event	218 (96.0)	142 (92.8)	277 (93.9)	419 (93.5)
Deaths	0	0	0	0
Non-fatal TEAE SAE	14 (6.2)	9 (5.9)	24 (8.1)	33 (7.4)
Study drug discontinuations due to AE	7 (3.1)	7 (4.6)	13 (4.4)	20 (4.5)
Includes data from studies OB-303/305 Source: OB-305 CSR Table 52				

Non-fatal Serious Adverse Events (SAE)

There were 47 (7.0%) subjects who experienced treatment-emergent non-fatal SAEs during the 2-year study period. Twenty-five subjects had a treatment-emergent SAE that occurred during the second year of the study: 9 (4.0%) in the placebo group, 4 (2.6%) in the mid-dose PHEN/TPM group, and 12 (4.1%) in the high-dose PHEN/TPM group. The table below lists the treatment-emergent non-fatal SAEs by system organ class (SOC).

Table 28: Non-fatal SAE by system organ class – 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Total	14 (6.2)	9 (5.9)	24 (8.1)	33 (7.4)
Cardiac disorders	0	3 (2.0)	3 (1.0)	6 (1.3)
Endocrine disorders	0	1 (0.7)	0	1 (0.2)
Gastrointestinal disorders	1 (0.4)	0	2 (0.7)	2 (0.4)
General disorders and administration site conditions	2 (0.9)	0	0	0
Hepatobiliary disorders	0	1 (0.7)	2 (0.7)	3 (0.7)
Immune system disorders	1 (0.4)	0	0	0
Infections and infestations	4 (1.8)	2 (1.3)	6 (2.0)	8 (1.8)
Injury, Poisoning, and procedural complications	2 (0.9)	0	0	0
Investigations	0	0	1 (0.3)	1 (0.2)
Musculoskeletal and connective tissue disorders	2 (0.9)	0	5 (1.7)	5 (1.1)
Neoplasms benign, malignant and unspecified	1 (0.4)	1 (0.7)	1 (0.3)	2 (0.4)
Nervous system disorders	1 (0.4)	1 (0.7)	3 (1.0)	4 (0.9)
Psychiatric disorders	1 (0.4)	0	0	0

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Renal and urinary disorders	1 (0.4)	0	2 (0.7)	2 (0.4)
Reproductive system and breast disorders	1 (0.4)	0	5 (1.7)	5 (1.1)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (0.3)	1 (0.2)
Vascular disorders	1 (0.4)	0	0	0
Source: Applicant's Post-text Table 14.4.1.41 OB-305 CSR Includes data from OB-303 and OB-305				

The largest numerical imbalance in SAEs between PHEN/TPM-treated and placebo-treated groups was in the cardiac disorders SOC. The following table is a breakdown of the preferred terms within the cardiac disorders SOC occurring over the 2-year period. Of these six events, only two (preferred terms myocardial infarction and acute myocardial infarction) occurred in the second year of treatment.

Table 29: Number (%) of treatment-emergent SAEs in the cardiac disorders SOC by preferred term – 2-year cohort (safety set)

SOC Preferred term	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Cardiac disorders	0	3 (2.0)	3 (1.0)	6 (1.3)
Myocardial infarction	0	1 (0.7)	1 (0.3)	2 (0.4)
Acute coronary syndrome	0	0	1 (0.3)	1 (0.2)
Acute myocardial infarction	0	0	1 (0.3)	1 (0.2)
Angina pectoris	0	0	1 (0.3)	1 (0.2)
Atrial fibrillation	0	1 (0.7)	0	1 (0.2)
Tachycardia	0	1 (0.7)	0	1 (0.2)
Source: Supporting Table 14.4.1.41, Pg 580 OB-305 CSR				

Further discussion regarding major adverse cardiovascular events in the entire PHEN/TPM clinical development program is provided in the cardiovascular risk assessment section of this briefing document.

Treatment-emergent adverse events (TEAE)

The organ systems with the highest proportion of subjects experiencing a TEAE over the 2-year study period were Infections and infestations (71.6%), Gastrointestinal disorders (49.0%), and Musculoskeletal and Connective Tissue disorders (40.9%).

The organ system classifications with a higher proportion of PHEN/TPM-treated subjects with a TEAE compared to placebo-treated subjects are listed in Table 30.

Table 30: Greater proportion of PHEN/TPM-treated with TEAE by SOC compared to placebo-treated – 2-year cohort (safety set)

SOC	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Gastrointestinal disorders	86 (37.9)	78 (51.0)	167 (56.6)	245 (54.7)
Nervous system disorders	62 (27.3)	59 (38.6)	138 (46.8)	197 (44.0)
Respiratory, thoracic, and mediastinal disorders	48 (21.1)	36 (23.5)	85 (28.8)	121 (27.0)
Psychiatric disorders	46 (20.3)	38 (24.8)	73 (24.7)	111 (24.8)
Skin and subcutaneous disorders	44 (19.4)	38 (24.8)	74 (25.1)	112 (25.0)
General disorders and administration site conditions	39 (17.2)	29 (19.0)	70 (23.7)	99 (22.1)
Eye disorders	34 (15.0)	28 (18.3)	56 (19.0)	84 (18.8)
Reproductive system and breast disorders	17 (7.5)	14 (9.2)	32 (10.8)	46 (10.3)
Ear and labyrinth disorders	12 (5.3)	11 (7.2)	22 (7.5)	33 (7.4)
Hepatobiliary disorders	2 (0.9)	3 (2.0)	5 (1.7)	8 (1.8)
Source: Supporting Table 14.4.1.3, OB-305 CSR, Pg 32 Data from studies OB-303 and OB-305				

The TEAEs listed by preferred term that occurred in at least 2% of PHEN/TPM-treated subjects and more frequently in both the mid- and high-dose PHEN/TPM group compared to placebo are listed in Table 31.

Table 31: TEAE occurring ≥2% and higher in PHEN/TPM-treated vs. placebo-treated – 2-year cohort (safety set)

Preferred term	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Constipation	22 (9.7)	34 (22.2)	67 (22.7)	101 (22.5)
Paraesthesia	6 (2.6)	22 (14.4)	66 (22.4)	88 (19.6)
Sinusitis	31 (13.7)	24 (15.7)	62 (21.0)	86 (19.2)
Dry Mouth	6 (2.6)	22 (14.4)	61 (20.7)	83 (18.5)
Dysgeusia	4 (1.8)	18 (11.8)	40 (13.6)	58 (12.9)
Insomnia	22 (9.7)	19 (12.4)	34 (11.5)	53 (11.8)
Influenza	19 (8.4)	21 (13.7)	31 (10.5)	52 (11.6)
Diarrhea	14 (6.2)	15 (9.8)	30 (10.2)	45 (10.0)
Procedural pain	10 (4.4)	14 (9.2)	28 (9.5)	42 (9.4)
Bronchitis	14 (6.2)	17 (11.1)	23 (7.8)	40 (8.9)

Preferred term	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Nausea	16 (7.0)	13 (8.5)	22 (7.5)	35 (7.8)
Cough	7 (3.1)	11 (7.2)	23 (7.8)	34 (7.6)
Dizziness	8 (3.5)	11 (7.2)	21 (7.1)	32 (7.1)
Fatigue	13 (5.7)	9 (5.9)	21 (7.1)	30 (6.7)
Alopecia	4 (1.8)	8 (5.2)	17 (5.8)	25 (5.6)
Osteoarthritis	8 (3.5)	8 (5.2)	12 (4.1)	20 (4.5)
Muscle strain	8 (3.5)	8 (5.2)	12 (4.1)	20 (4.5)
Rash	8 (3.5)	7 (4.6)	13 (4.4)	20 (4.5)
Gastroesophageal reflux disease	7 (3.1)	6 (3.9)	13 (4.4)	19 (4.2)
Hypokalemia	1 (0.4)	5 (3.3)	14 (4.7)	19 (4.2)
Myalgia	7 (3.1)	5 (3.3)	12 (4.1)	17 (3.8)
Contusion	6 (2.6)	7 (4.6)	10 (3.4)	17 (3.8)
Decreased appetite	4 (1.8)	7 (4.6)	10 (3.4)	17 (3.8)
Irritability	3 (1.3)	3 (2.0)	13 (4.4)	16 (3.6)
Hypoesthesia	3 (1.3)	6 (3.9)	10 (3.4)	16 (3.6)
Eye pain	4 (1.8)	5 (3.3)	10 (3.4)	15 (3.3)
Disturbance in attention	1 (0.4)	5 (3.3)	9 (3.1)	14 (3.1)
Asthma	0	4 (2.6)	10 (3.4)	14 (3.1)
Ear infection	5 (2.2)	5 (3.3)	9 (3.1)	14 (3.1)
Tooth infection	4 (1.8)	6 (3.9)	7 (2.4)	13 (2.9)
Upper abdominal pain	3 (1.3)	3 (2.0)	9 (3.1)	12 (2.7)
Joint injury	2 (0.9)	3 (2.0)	8 (2.7)	11 (2.5)
Nasal congestion	5 (2.2)	4 (2.6)	7 (2.4)	11 (2.5)
Hemorrhoids	1 (0.4)	2 (1.3)	8 (2.7)	10 (2.2)
Cellulitis	3 (1.3)	3 (2.0)	7 (2.4)	10 (2.2)
Dry eye	2 (0.9)	4 (2.6)	6 (2.0)	10 (2.2)
Tinnitus	1 (0.4)	2 (1.3)	8 (2.7)	10 (2.2)
Pruritus	0	5 (3.3)	5 (1.7)	10 (2.2)
Vertigo	3 (1.3)	4 (2.6)	5 (1.7)	9 (2.0)
Epistaxis	3 (1.3)	5 (3.3)	4 (1.4)	9 (2.0)
Erectile dysfunction	1 (0.4)	1 (0.7)	7 (2.4)	8 (1.8)
Carpal tunnel syndrome	3 (1.3)	3 (2.0)	5 (1.7)	8 (1.8)
Asthenia	0	2 (1.3)	6 (2.0)	8 (1.8)
Lower abdominal pain	0	4 (2.6)	1 (0.3)	5 (1.1)
Syncope	1 (0.4)	3 (2.0)	2 (0.7)	5 (1.1)
Urticaria	2 (0.9)	3 (2.0)	3 (1.0)	6 (1.3)
Asthenia	0	2 (1.3)	6 (2.0)	8 (1.8)
Source: Applicant's Supporting Table 14.4.1.3, Pg OB-305 CSR				

Discontinuation of study medication due to adverse events

Since all subjects eligible for the 1-year extension period had to be on treatment at the end of the first year, all of the study drug discontinuations occurred in the second year. Twenty-seven (4.0%) subjects had a TEAE which resulted in study drug discontinuation (SDAE). Table 32 lists all the SDAEs grouped by system organ class and preferred term. The most common organ systems that resulted in a SDAE were nervous system, psychiatric, and eye disorders. There were no SDAEs in the placebo group that occurred at an incidence of $\geq 0.5\%$. In the high-dose PHEN/TPM group, four subjects (1.4%) discontinued due to a psychiatric disorder (depression or anxiety) versus one individual (0.4%) in the placebo due to depression.

Table 32: Number and frequency of subjects with SDAE by SOC and preferred term – 2-year cohort (safety set)

System Organ Class Preferred term	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Total	7 (3.1)	7 (4.6)	13 (4.4)	20 (4.4)
Nervous System Disorders	1 (0.4)	0	4 (1.4)	4 (0.9)
Amnesia	0	0	1 (0.3)	1 (0.2)
Hemorrhage intracranial	1 (0.4)	0	0	0
Judgement impaired	0	0	1 (0.3)	1 (0.2)
Memory impairment	0	0	1 (0.3)	1 (0.2)
Paraesthesia	0	0	1 (0.3)	1 (0.2)
Psychiatric disorders	1 (0.4)	0	4 (1.4)	4 (0.9)
Depression	1 (0.4)	0	3 (1.0)	3 (0.7)
Anxiety	0	0	1 (0.3)	1 (0.2)
Eye disorders	1 (0.4)	1 (0.7)	2 (0.7)	3 (0.7)
Vision blurred	1 (0.4)	0	1 (0.3)	1 (0.2)
Cataract	0	1 (0.7)	0	1 (0.2)
Eye pain	0	0	1 (0.3)	1 (0.2)
Gastrointestinal disorders	0	2 (1.3)	1 (0.3)	3 (0.7)
Abdominal pain	0	0	1 (0.3)	1 (0.2)
Diarrhea	0	1 (0.7)	0	1 (0.2)
Hypoaesthesia oral	0	1 (0.7)	0	1 (0.2)
Investigations	1 (0.4)	0	1 (0.3)	1 (0.2)
Heart rate irregular	1 (0.4)	0	0	0
TB skin test positive	0	0	1 (0.3)	1 (0.2)
Musculoskeletal and connective tissue disorders	0	2 (1.3)	0	2 (0.4)
Arthralgia	0	1 (0.7)	0	1 (0.2)
Muscle spasms	0	1 (0.7)	0	1 (0.2)

System Organ Class Preferred term	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
Renal and urinary disorders	1 (0.4)	0	1 (0.3)	1 (0.2)
Nephrolithiasis	0	0	1 (0.3)	1 (0.2)
Nephrotic syndrome	1 (0.4)	0	0	0
Cardiac disorders	0	1 (0.7)	0	1 (0.2)
Myocardial infarction	0	1 (0.7)	0	1 (0.2)
General disorders and administration site	1 (0.4)	0	0	0
Fatigue	1 (0.4)	0	0	0
Hepatobiliary disorders	0	1 (0.7)	0	1 (0.2)
Cholecystitis	0	1 (0.7)	0	1 (0.2)
Immune system disorders	1 (0.4)	0	0	0
Drug hypersensitivity	1 (0.4)	0	0	0
Infections and infestation	0	1 (0.7)	0	1 (0.2)
Pyelonephritis	0	1 (0.7)	0	1 (0.2)
Skin and subcutaneous tissue disorders	0	1 (0.7)	0	1 (0.2)
Hypoaesthesia facial	0	1 (0.7)	0	1 (0.2)
Vascular disorder	1 (0.4)	0	0	0
Hypotension	1 (0.4)	0	0	0
Source: Applicant's Post-text Table 14.4.1.43, OB-305 CSR				

Targeted Medical Events

The applicant and the Division agreed on several Targeted Medical Events (TME) (Table 33) 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 33: 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	

For all of the TMEs, there was a higher frequency in subjects treated with PHEN/TPM than subjects treated with placebo. By TME subclass, there was at least a 1% difference between PHEN/TPM-treated subjects and placebo-treated subjects for the subclasses of sleep disorders, anxiety, attention, memory impairment, ophthalmic, and psychomotor disorders.

Table 34: Number (%) of subjects with treatment-emergent Targeted Medical Events by class and subclass – 2-year cohort (safety set)

TME Class TME Subclass	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	PHEN/TPM Total N=448 n (%)
TOTAL	64 (28.2)	60 (39.2)	102 (34.6)	162 (36.2)
Psychiatric disorders	42 (18.5)	33 (21.6)	70 (23.7)	103 (23.0)
Sleep disorders	25 (11.0)	22 (14.4)	38 (12.9)	60 (13.4)
Depression	18 (7.9)	6 (3.9)	24 (8.1)	30 (6.7)
Anxiety	7 (3.1)	10 (6.5)	28 (9.5)	38 (8.5)
Cardiovascular disorders	12 (5.3)	12 (7.8)	15 (5.1)	27 (6.0)
Cardiac arrhythmia	11 (4.8)	10 (6.5)	12 (4.1)	22 (4.9)
Ischemic heart disease	1 (0.4)	2 (1.3)	3 (1.0)	5 (1.1)
Cognitive disorders	5 (2.2)	10 (6.5)	17 (5.8)	27 (6.0)
Attention	1 (0.4)	5 (3.3)	9 (3.1)	14 (3.1)
Memory Impairment	2 (0.9)	3 (2.0)	6 (2.0)	9 (2.0)
Other cognitive disorders NOS	2 (0.9)	1 (0.7)	4 (1.4)	5 (1.1)
Language	0	2 (1.3)	1 (0.3)	3 (0.7)
Oligohydrosis and hyperthermia	9 (4.0)	9 (5.9)	13 (4.4)	22 (4.9)
Oligohydrosis/hyperthermia	9 (4.0)	9 (5.9)	13 (4.4)	22 (4.9)
Ophthalmic disorders	4 (1.8)	6 (3.9)	12 (4.1)	18 (4.0)
Ophthalmic disorders	4 (1.8)	6 (3.9)	12 (4.1)	18 (4.0)
Psychomotor disorders	0	1 (0.7)	4 (1.4)	5 (1.1)
Psychomotor disorders	0	1 (0.7)	4 (1.4)	5 (1.1)
Source: Supporting Table 14.4.1.11, OB-305 CSR, Pg 405				

Psychiatric disorders TME

The psychiatric disorders TME were divided into four subclasses: Sleep, Anxiety, Depression, and Suicide/self injury which are described below and in Table 35.

Sleep disorders subclass

The majority of the TEAEs occurring in the sleep disorder subclass were related to insomnia and most were mild in severity. There was only one case of a severe episode of sleep disturbance in a high-dose PHEN/TPM-treated individual. There were no serious TEAEs within this subclass and no individual discontinued study drug due to a sleep disorder AE (Table 35). A smaller percentage of PHEN/TPM-treated subjects had resolution of their sleep disorder compared to placebo-treated subjects.

Anxiety subclass

PHEN/TPM-treated subjects were approximately 3 times more likely to experience a TEAE related to anxiety compared to placebo-treated subjects. Within this subclass, a dose-response relationship was suggested for the preferred term of anxiety (placebo 3.1%, mid-dose 3.9%, high-dose 5.1%) and irritability (placebo 1.3%, mid-dose 2.0%, high-dose 4.4%). Overall, the majority of the events were mild in severity; however, three severe anxiety related events occurred in the high-dose PHEN/TPM-treated group versus none in the placebo-treated group. Only one individual discontinued study drug due to an anxiety AE (high-dose PHEN/TPM). Overall, a higher proportion of PHEN/TPM-treated subjects had their anxiety resolve compared to placebo-treated subjects.

Depression subclass

The incidence of depression was lower or very similar between the PHEN/TPM-treated and placebo-treated groups. The majority of the events in the PHEN/TPM-treated group were mild in severity and resolved. There was one serious adverse event in a placebo-treated individual within this targeted medical event. The preferred term within this subclass that occurred with the highest frequency was depression. Of the subjects with a depression-related TEAE, 3 (12.5%) PHEN/TPM-treated and 1 (5.6%) placebo-treated subject discontinued the study drug due to this event.

Suicide/self-injury subclass

There were no events within this subclass in the 2-year cohort.

Table 35: Subjects with Psychiatric TME by subclass – 2-year cohort (safety set)

Psychiatric disorders TME	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Patients with sleep disorders¹	25 (11.0)	22 (14.4)	38 (12.9)
Discontinued study drug	0	0	0
Resolved	21 (84.0)	18 (81.8)	28 (73.7)
Time to first onset [Mean (SD)](days)	208.2 (224.9)	265.9 (260.4)	197.0 (201.8)
Duration [Mean (SD)] (days) ¹	133.4 (184.2)	148.2 (186.8)	174.9 (220.2)
Patients with anxiety	7 (3.1)	10 (6.5)	28 (9.5)
Discontinued study drug	0	0	1 (3.6)
Resolved	3 (42.9)	7 (70.0)	22 (78.6)
Time to first onset [Mean (SD)] (days)	142.0 (148.4)	290.8 (306.8)	206.7 (200.8)
Duration [Mean (SD)] (days) ¹	351.3 (292.0)	118.6 (83.6)	178.1 (190.0)
Patients with depression	18 (7.9)	6 (3.9)	24 (8.1)

Psychiatric disorders TME	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Discontinued study drug	1 (5.6)	0	3 (12.5)
Resolved	13 (72.2)	5 (83.3)	20 (83.3)
Time to first onset [Mean (SD)](days)	205.2 (170.5)	465.3 (269.3)	276.5 (214.7)
Duration [Mean (SD)] (days) ²	201.7 (235.0)	44.7 (70.0)	159.6 (176.0)
Source: Supporting Table 14.4.1.15, 17, 19 OB-305 CSR, Pg 424-448 ¹ Percentage in the bolded rows is calculated using number of subjects in the column heading as the denominator. All other percentages are calculated using the number of subjects in each treatment group experiencing the given TME. ² For events with unknown stop date, the last dose date + 28 days is used.			

Assessment of Depression

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 3). 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 greater than zero. 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 36). Current recommendations suggest a score of 10 as a screening cut point for depression, which has sensitivity for major depression of 88% and specificity of 88%.² Subjects were eligible to enroll if their baseline scores were <10 and they had a 0 response to Question 9. Further clinical review and assessment was required if subjects had a PHQ score of ≥ 15 or a positive response to Question 9.

² Kroenke, K, Spitzer R. The PHQ-9: A new depression diagnostic and severity measure. Psychiatric Annals 2002; 32: 1-7.

Figure 3: 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 36: 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 2-year safety cohort at baseline, the majority of subjects had no clinical depression by PHQ-9 score (Table 37).

Table 37: PHQ-9 depression severity at baseline - 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
None	169 (74.4)	124 (81.0)	230 (78.0)
Mild	46 (20.3)	22 (14.4)	56 (19.0)
Moderate	1 (0.4)	0	0
Moderately Severe	0	0	0
Severe	0	0	0
Missing	11 (4.8)	7 (4.6)	9 (3.1)

Source: Supporting Table 14.4.4.29, OB-305 CSR, Pg 97

The numbers and percentages of subjects with a worsening shift in PHQ-9 depression severity (from baseline to highest score) of two or more categories are shown in Table 38. Overall, there were a smaller proportion of PHEN/TPM-treated subjects with a worsening shift compared to the placebo-treated subjects.

Table 38: PHQ-9 worsening depression severity score¹ – 2-year cohort (safety set)

	Placebo n (%) N=227	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Total subjects with worsening shift	9 (4.0)	2 (1.3)	7 (2.4)
None to Moderate	4 (1.8)	2 (1.3)	4 (1.4)
None to Moderately severe	2 (0.9)	0	2 (0.7)
None to Severe	1 (0.4)	0	0
Mild to Moderately severe	1 (0.4)	0	0
Mild to Severe	1 (0.4)	0	0
Moderate to Severe	0	0	0
Missing to Moderately severe	0	0	1 (0.3)

¹ Increase of two or more categories
Data from studies OB-303/305
Source: Supporting Table 14.4.4.29, OB-305 CSR, Pg 97

During conduct of the 2-year study, a small and similar percentage of subjects scored a positive response to Question 9 (placebo 1.3%, mid-dose PHEN/TPM 1.3%, high-dose PHEN/TPM 0.7%) which corresponds to: “Thoughts you would be better off dead or of hurting yourself in some way.” There were five (2.2%) placebo-treated and 3 (1.0%) high-dose PHEN/TPM-treated subjects with a PHQ-9 score ≥ 15 during the two-year study.

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 or emergence of serious suicidal ideation that occurred during study treatment.

For overall suicidality, which is a combination of suicidal behavior and suicidal ideation, there were six subjects (3 in the placebo group (1.3%), 1 in the mid-dose PHEN/TPM group (0.7%), and 2 in the high-dose PHEN/TPM group (0.7%) which responded “YES” to either “wish to be dead” or “non-specific suicidal thoughts” (Table 39).

Table 39: Number and frequency of suicidal behavior and ideation “YES” responses – 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Suicidality (Behavior or Ideation)	3 (1.3)	1 (0.7)	2 (0.7)
Any Suicidal Behavior	0	0	0
Actual Attempt	0	0	0
Aborted Attempt	0	0	0
Interrupted Attempt	0	0	0
Preparatory Acts or Behavior	0	0	0
Any Suicidal Ideation	3 (1.3)	1 (0.7)	2 (0.7)
Wish to be Dead	3 (1.3)	1 (0.7)	2 (0.7)
Non-specific Suicidal Thoughts	2 (0.9)	1 (0.7)	2 (0.7)
Suicidal Thoughts with Methods	1 (0.4)	0	2 (0.7)
Ideation with intent	0	0	0
Ideation with plan and intent	0	0	0
Source: Supporting Table 14.4.4.32, Pg 105, OB-305 CSR Data from studies OB-303/305 All C-SSRS measurements obtained during the double-blind treatment period of studies OB-303/305 are considered. Subjects 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.			

Other items the C-SSRS evaluates include the emergence or worsening of suicidal ideation. Emergence is defined as the number of subjects who had no suicidal ideation at baseline who develop any type of ideation during treatment. Worsening of suicidal ideation is defined as the number of participants whose most severe suicidal ideation rating is more severe than at baseline. This analysis demonstrated that the number of subjects with an emergence or worsening of suicidal ideation was very small and similar between groups.

Cognitive disorders TME Class

This class was subdivided into Attention, Memory impairment, Language, and Other NOS and are described below and in Table 40.

Attention subclass

PHEN/TPM-treated subjects were almost seven times more likely to experience a TEAE related to an attention disorder compared to placebo-treated subjects. The majority of the events were mild in severity and there were no serious events within this subclass. All of the attention disturbances resolved. Three subjects treated with PHEN/TPM had their dose reduced as a result of the event. The time to onset of events occurred earlier in the PHEN/TPM-treated group compared to the placebo-treated group.

Memory impairment subclass

PHEN/TPM-treated subjects were two times more likely to experience a TEAE related to memory impairment compared to placebo-treated subjects. No events were considered serious and the majority of events were rated as mild in severity; however, more high-dose PHEN/TPM-treated subjects experienced a moderate or severe incidence of memory impairment and discontinued study drug due to impaired memory compared to mid-dose PHEN/TPM or placebo-treated subjects. Occurrence of memory impairment occurred for most subjects after the first four weeks of treatment.

A sample narrative of an individual discontinuing study drug due to worsening memory impairment is described below.

A 47-year-old Caucasian male with a history of obesity, was randomized to PHEN/TPM 15/92 mg in the OB-303 study on 26-Mar-2008 and signed informed consent for the OB-305 extension study on Study Day 393 (22-Apr-2009). On Study Day 431 (30-May-2009), the subject reported moderate impaired short term memory. On Study Day 679 (02-Feb-2010), the subject developed worsened impaired short term memory. The subject felt his lack of memory was beginning to seriously affect his ability to work. He frequently forgot what he was talking about while presenting in meetings and what he was working on in front of the computer. The subject intentionally skipped doses of study drug during the month of February when he had to speak in meetings. He also stated that his wife had noticed deterioration in his memory and had been having to “keep him straight” instead of the other way around, which was what was normal for them. The subject’s PHQ-9 scores ranged from 1 to 4 on three occasions. All C-SSRS responses throughout the study were negative. The study drug was permanently discontinued on Study Day 700 (23-Feb-2010). The subject recovered from the event on Study Day 743 (07-Apr-2010). The subject was withdrawn from the study due to the event on Study Day 757 (21-Apr-2010).

Language subclass

Three patients in the PHEN/TPM-treated group versus none in the placebo-treated group experienced either aphasia or dysarthria. No individual discontinued study drug due to this event and all were classified as mild. The onset of the event was within the first three months and all events resolved, however two subjects had their dose of PHEN/TPM reduced as a result of 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. The majority of the events were mild except for two subjects treated with high-dose PHEN/TPM with moderate events. The majority of the preferred terms were listed as a cognitive disorder or confusional state. One individual treated with high-dose PHEN/TPM discontinued study drug due to the event.

Table 40: Subjects with Cognitive TME by subclass – 2-year cohort (safety set)

Cognitive disorders TME	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Patients with attention disorders¹	1 (0.4)	5 (3.3)	9 (3.1)
Discontinued study drug	0	0	0
Resolved	1 (100.0)	5 (100.0)	9 (100.0)
Time to first onset [Mean (SD)] (days)	341.0	8.4 (6.6)	46.2 (61.8)
Duration [Mean (SD)] (days) ²	55.0	21.6 (20.8)	97.3 (87.4)
Patients with memory disorders	2 (0.9)	3 (2.0)	6 (2.0)
Discontinued study drug	0	0	2 (33.3)
Resolved	1 (50.0)	3 (100.0)	5 (83.3)

Cognitive disorders TME	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Time to first onset [Mean (SD)] (days)	119.5 (65.8)	124.7 (135.4)	106.0 (160.3)
Duration [Mean (SD)] (days) ²	422.0 (407.3)	260.3 (224.4)	295.2 (149.5)
Patients with language disorders	0	2 (1.3)	1 (0.3)
Discontinued study drug	0	0	0
Resolved	0	2 (100.0)	1 (100.0)
Time to first onset [Mean (SD)] (days)	0	13.5 (6.4)	81.0
Duration [Mean (SD)] (days) ²	0	347.0 (479.4)	33.0
Patients with other cognitive disorders NOS	2 (0.9)	1 (0.7)	4 (1.4)
Discontinued study drug	0	0	1 (25.0)
Resolved	2 (100.0)	1 (100.0)	4 (100.0)
Time to first onset [Mean (SD)] (days)	225.5 (308)	25	128.8 (225.7)
Duration [Mean (SD)] (days) ²	36.5 (16.3)	32	73.8 (69.3)
Source: Supporting Table 14.4.1.25, 27, 29, 31 OB-305 CSR, Pg 484-520			
¹ Percentage in the bolded rows is calculated using number of subjects in the column heading as the denominator. All other percentages are calculated using the number of subjects in each treatment group experiencing the given TME			
² For events with unknown stop date, the last dose date + 28 days is used			

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-dose PHEN/TPM treated subjects compared to placebo-treated subjects (Table 41). A similar frequency of events occurred in the high-dose PHEN/TPM and placebo groups. The majority of events were rated as mild in severity. In the 2-year cohort, two subjects in the mid-dose PHEN/TPM group had a serious adverse event related to a cardiac arrhythmia. The majority of the adverse events were related to palpitations, increased heart rate, and tachycardia.

Table 41: Subjects with Cardiac TME by subclass – 2-year cohort (safety set)

Cardiac disorders TME	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Patients with cardiac arrhythmia¹s	11 (4.8)	10 (6.5)	12 (4.1)
Discontinued study drug	1	0	0
Resolved	8 (72.7)	8 (80.0)	11 (91.7)
Time to first onset [Mean (SD)] (days)	409.2 (179.1)	251.0 (306.7)	198.8 (263.3)
Duration [Mean (SD)] (days) ²	71.8 (117.5)	30.1 (70.5)	95.3 (149.2)
Patients with ischemic heart disease	1 (0.4)	2 (1.3)	3 (1.0)
Discontinued study drug	0	1 (50.0)	0
Serious adverse event	0	1 (50.0)	3 (100.00)

Cardiac disorders TME	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Resolved	0	0	1 (33.3)
Time to first onset Mean (SD) (days)	97.0	424.5 (309.0)	403.7 (157.6)
Duration [Mean (SD)] (days) ²	492.0	301.0 (384.7)	322.3 (270.3)
Source: Supporting Table 14.4.1.21, 23 OB-305 CSR, Pg 460, 472			
¹ Percentage in the bolded rows is calculated using number of subjects in the column heading as the denominator. All other percentages are calculated using the number of subjects in each treatment group experiencing the given TME			
² For events with unknown stop date, the last dose date + 28 days is used			

Ischemic heart disease subclass

Overall, within the ischemic heart disease subclass, a higher percentage of events occurred in the PHEN/TPM-treated groups (placebo 0.4%, PHEN/TPM total 1.1%). The majority of the events within this subclass were rated as severe. No subjects in the placebo group and four subjects in the PHEN/TPM group experienced a non-fatal SAE related to cardiac ischemia. The subjects, preferred term, and narratives are presented below.

Table 42: Listing of subjects with SAEs from ischemic heart disease subclass 2-year cohort

Mid dose PHEN/TPM	
131-059	Myocardial infarction
High-dose PHEN/TPM	
131-042	Myocardial infarction*
178-121	Acute myocardial infarction
199-037	Acute coronary syndrome* Angina pectoris*
* The SAE began during study OB-303	

Subject 131-059: myocardial infarction

A 49-year-old Caucasian male with a history of obesity, was randomized to PHEN/TPM 7.5/46 mg in the OB-303 study on (b) (6) and signed informed consent for the OB-305 extension study on Study Day 399 (b) (6). On Study Day 646 (b) (6), the subject was admitted to the hospital for evaluation and treatment of a 3-day history of chest pain, nausea, and vomiting. Laboratory results revealed a creatine phosphokinase of 233 and 133, a troponin of 0.43 and a CK-MB of 4.10 (units and normal ranges not provided). On Study Day 647 (b) (6), the subject's chest pain worsened; an electrocardiogram showed poor R wave progression and non-specific ST-T wave abnormalities, and laboratory results revealed a troponin of 3.18 and 4.91 and a CK-MB of 19.90. The subject was subsequently diagnosed with a myocardial infarction. The subject underwent a cardiac catheterization with placement of two stents in the right coronary and left circumflex arteries. Intermediate left anterior descending artery disease with normal left ventricle function was noted. On Study Day 646 (b) (6), laboratory results revealed a troponin of 4.277. Treatment of the event included aspirin, lorazepam, morphine, nitroglycerin, clopidogrel, sulfate, Protonix, and pravastatin. The subject was discharged from the hospital and recovered from the event on Study Day 649 (b) (6). The study drug was permanently discontinued on Study Day 646 (b) (6). The subject was withdrawn from the study due to the event on Study Day 659 (b) (6). The subject's medical history includes cervical fusion C1-C2, degenerative joint disease (knees), depression, fusion C5-C6, left shoulder rotator cuff surgery, right knee surgery, scoliosis, dyslipidemia, hypertension, and seasonal allergies. Concomitant medications included atenolol and acetaminophen. The investigator considered the event of myocardial infarction as moderate in severity and not related to study drug.

Subject 131-042/a 68-year-old Caucasian male with a history of obesity, signed informed consent on 22-Jan-2008 was randomized to PHEN/TPM 15/92 mg on (b) (6). On Study Day 342 (b) (6), the subject presented to the emergency room after having an episode of chest pain. On Study Day 343 (b) (6), 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) (6), at 7:30, troponin was 17.41 ng/mL. A diagnosis of myocardial infarction was made. On Study Day 344 (b) (6), 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) (6), 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) (6). The study drug was interrupted from Study Day 333 (b) (6) to Study Day 373 (b) (6). 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. The investigator considered the event of myocardial infarction as severe in severity and not related to study drug.

Subject 178-121: non-ST elevation myocardial infarction, acute ischemic stroke, acute renal failure, influenza type A, pneumonia, and respiratory failure

A 38-year-old African female with a history of obesity, was randomized to PHEN/TPM 15/92 mg in the OB-303 study on (b) (6) and signed informed consent for the OB-305 extension study on Study Day 392 (b) (6). On an unknown date in 2009, the subject was diagnosed with a hiatal hernia during work-up for an elective gastric banding. On Study Day 582 (b) (6), the subject underwent gastric banding with concurrent hiatal hernia repair. On the following day, the subject became less responsive and more obtunded. On Study Day 584 (b) (6), the subject's husband noted that her respirations were very shallow and she was unresponsive. Emergency medical services were called. The subject was intubated and administered naloxone hydrochloride. A chest x-ray revealed perihilar infiltrates with atelectasis. Physical examination revealed a blood pressure of 135/95 mmHg, pulse of 60 bpm, bilateral rhonchi upon auscultation, normal heart sounds, and an unremarkable abdomen. Initial bedside cardiac markers were positive with creatine phosphokinase of 7647 and troponin of 9.97 (units and normal ranges not provided). An electrocardiogram demonstrated sinus tachycardia at 152 bpm with diffuse nonspecific ST-T changes. A computerized tomogram scan of the brain without contrast revealed a 14 mm hypodensity in the left frontal lobe near the anterior portion of the internal capsule, representing a possible acute to subacute infarct. There was no evidence of intracranial hemorrhage. Laboratory results revealed creatinine of 1.7 (units and normal ranges not provided) and positive influenza A antigen. The subject was subsequently diagnosed with non-ST elevation myocardial infarction, acute ischemic stroke, acute renal failure, influenza type A, pneumonia, and respiratory failure. On Study Day 585 (b) (6), an echocardiogram revealed preserved left ventricular function and normal sized chambers. On the following day, an electroencephalogram was moderately abnormal due to intermixed slower frequencies even during the apparent awakened state, photic reactivity, findings suggested a moderate diffuse cortical dysfunction without any localizing features, and no distinguishing portion of the trace to suggest an etiology. On Study Day 587 (b) (6), a magnetic resonance imaging scan of the brain showed restricted diffusion in the globus pallidus bilaterally. Sputum and blood cultures were negative. Treatment of the event included propofol, oseltamivir phosphate, levofloxacin, ceftriaxone, salbutamol sulfate, metoprolol tartrate, aspirin, sertraline, potassium chloride, hydrochlorothiazide, enoxaparin sodium, and Zosyn. The subject recovered from the event and was discharged from the hospital on Study Day 594 (b) (6). The study drug was permanently discontinued on Study Day 560 (b) (6). The subject was lost to follow-up. The subject's medical history includes acne, anemia, breast reduction, gastroesophageal reflux disease, headaches, insomnia, intermittent joint pain, menstrual cramps, migraines, nearsightedness, recurrent sinusitis, right elbow fracture, seasonal allergic rhinitis, hypertension, and tubal ligation. Concomitant medications included Alka Seltzer, candesartan, Excedrin migraine, fluticasone, Pamprin, olopatadine, omeprazole, cetirizine, valsartan, hydrochlorothiazide, Differin Gel 1%, ferrous sulfate, Fiber Choice, hydrocodone/acetaminophen, and multivitamin. The investigator considered the events of non-ST elevation myocardial infarction, acute ischemic stroke, acute renal failure, influenza type A, pneumonia, and respiratory failure as severe in severity and not related to study drug.

Subject 199-037/CWB, a 64-year-old Caucasian male with a history of obesity, signed informed consent on 17-Mar-2008 and was randomized to PHEN/TPM 15/92 mg on (b) (6). On Study Day 289 (b) (6), the subject experienced intermittent sharp chest pain and presented to the emergency room for evaluation and treatment. On that same date, the subject underwent a cardiac single photon emission computed tomography stress test, which revealed possible reversible ischemia. An electrocardiogram revealed possible high lateral myocardial infarction and a second electrocardiogram revealed an anterolateral infarct (age undetermined). Laboratory testing revealed a creatine kinase (CK) of 80 IU/L, CK-MB of 2.5 ng/mL, and two troponin tests that were indeterminate at 0.5 ng/mL and 0.6 ng/mL (normal ranges not reported). The subject was discharged from the emergency room on a beta-blocker and recommendation to follow up with his primary care physician. On Study Day 298 (b) (6), the subject was admitted to the hospital for the cardiac catheterization, which revealed diffuse atherosclerotic plaque throughout the coronary tree and a high-grade lesion in the first diagonal suitable for intervention. The subject was subsequently diagnosed with coronary artery disease and underwent single vessel balloon angioplasty of the diagonal artery. Additional treatment of the event included metoprolol, clopidogrel, and nitroglycerin. The subject recovered from the event on Study Day 299 (b) (6) and was discharged from the hospital on that same date. The study drug was continued and the subject continued in the study. On Study Day 360 (b) (6), the subject experienced chest pain with exertion. On Study Day 362 (b) (6), the subject experienced the same pain two to three times associated with an elevated blood pressure (blood pressure unknown), warmth, and flushing. On the same date, the subject went to the emergency room and was admitted for observation. Vital signs included blood pressure of 122/72 mmHg and heart rate of 66 bpm. The physical examination was within normal limits, and a chest X-ray and electrocardiogram were unremarkable. Laboratory tests included creatine kinase (CK) of 122 IU/L, CK-MB of 3.0 ng/mL, and troponin I of 0.03 ng/mL (normal ranges not reported). Treatment of the event included nitroglycerin, heparin, metoprolol, and isosorbide mononitrate. On Study Day 363 (b) (6), the subject was discharged from the hospital. On Study Day 364 (b) (6), the subject followed up with his cardiologist. On Study Day 365 (b) (6), the subject underwent a myocardial perfusion stress test, which revealed angina pectoris. On Study Day 381 (b) (6) the subject was admitted to the hospital for a left heart catheterization procedure with left ventriculography and coronary angiography. Coronary angiography found stenosis of the first diagonal branch of the LAD, which was revascularized following the placement of three TAXUS drug-eluting stents. The subject recovered from the event and was discharged from the hospital on Study Day 382 (b) (6). The subject was on every-other-day dosing. The study drug was interrupted only on Study Day 362 (b) (6). The subject continued in the study. The subject's medical history includes past tobacco use (cigarettes), dyslipidemia, hardness of hearing, asthma, gastroesophageal reflux disease, Escherichia coli in prostate, right knee meniscus tear with surgery, mild depression, indoor and outdoor allergies, right elbow bone chip and surgery, vertigo, appendectomy, benign prostatic hypertrophy, insomnia, and pilonidal cyst. Concomitant medications included diphenhydramine, meclizine, alfuzosin, fish oil, Advair, azelastine, dimenhydrinate, lovastatin, aspirin, esomeprazole, ipratropium, multivitamin, montelukast, and glucosamine/chondroitin. The investigator considered the event of acute coronary syndrome as severe in severity and not related to study drug, and the event of angina pectoris as moderate in severity and not related to study drug.

Ophthalmic disorders Class

Acute myopia and secondary angle closure glaucoma are listed in the warnings and precautions section of the topiramate label. Subjects 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 subjects (mid-dose 3.9%, high-dose 4.1%) compared to placebo-treated subjects (1.8%). Subjects treated with PHEN/TPM were two times more likely to report eye pain than those treated with placebo. Two PHEN/TPM-treated subjects reported an increase in intraocular pressure. The majority of events were rated as mild in severity and occurred after the first four weeks of treatment. No events were listed as serious; however, one high-dose treated individual discontinued study drug due to eye pain. The majority of the adverse events within this TME were related to eye pain.

Psychomotor disorders Class

The overall number of subjects reporting a TEAE within the psychomotor disorder class was small: 5 subjects treated with PHEN/TPM reported a psychomotor disorder compared to none treated with placebo. All of the events were rated as mild and the most common adverse event reported within this TME was psychomotor hyperactivity.

Drug Abuse/withdrawal Class

There were no TEAEs within this class reported in the 2-year cohort for any of the treatment groups.

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 TEAE, metabolic acidosis and acidosis-related AEs were uncommon. There were 7 subjects in the 2-year safety cohort who reported an AE of blood bicarbonate decreased (0.4%, placebo, 1.3% mid-dose, 1.4% high-dose).

Fasting blood chemistries including bicarbonate were evaluated at screening and at Weeks 4, 8, 16, 28, 40, 56, 84, 96, and at the end of treatment. There were no arterial blood gases obtained within the PHEN/TPM development program. There were no established intervention procedures for bicarbonate values less than 21 mEq/L. Mean serum bicarbonate increased approximately 0.7 mEq/L in the mid-dose PHEN/TPM group, 0.2 mEq/L in the high-dose PHEN/TPM group, and 2.2 mEq/L in the placebo group.

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 subjects that obtain a 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 subjects with a subnormal serum bicarbonate using the cutoffs of <21 mEq/L at any time (Table 43) and persistently (Table 44). Persistence was defined as two consecutive visits below the given threshold or a value below the given threshold at the final visit.

In the 2-year safety cohort, 28% of PHEN/TPM-treated subjects experienced at least one serum bicarbonate less than 21 mEq/L versus 4.0% of placebo-treated subjects. A higher proportion of subjects experienced a low serum bicarbonate value in the first year of treatment.

Table 43: Number (%) of subjects with serum bicarbonate <21 mEq/L – 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	TOTAL PHEN/TPM N=448 n (%)
Weeks 0 to 108	9 (4.0)	35 (22.9)	90 (30.5)	125 (27.9)
Week 0 to 56	7 (3.1)	34 (22.2)	83 (28.1)	21 (4.7)
Week 56 to 108	2 (0.9)	6 (3.9)	15 (5.1)	21 (4.7)
Source: IR response submitted 1/18/12 submission number 0070				

The number of subjects with persistently abnormal serum bicarbonate values defined as low bicarbonate at 2 or more consecutive visits or a value below the given threshold at the final visit also demonstrates a dose response with PHEN/TPM treatment.

Table 44: Number (%) of subjects with persistently low serum bicarbonate – 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)	TOTAL PHEN/TPM N=448 n (%)
Serum bicarbonate	0	6 (3.9)	20 (6.8)	26 (5.8)

<21 mEq/L				
Serum bicarbonate <17 mEq/L	0	0	1 (0.3)	1 (0.2)
Decrease from baseline >5 mEq/L	4 (1.8)	20 (13.1)	48 (16.3)	68 (15.2)
Source: Supporting Table 14.4.4.15, Pg 32, OB-305 CSR Persistence defined as two or more consecutive visits or a value below the given threshold at the final visit Data from studies OB-303/305				

Vital signs

The following tables summarize the mean changes in SBP, DBP, heart rate, and rate-pressure product in subjects with a baseline and Week 108 measurement in the 2-year safety cohort. Table 46 presents the numbers and percentages of subjects with categorical increases in SBP, DBP, and heart rate at any time point during the 2-year study period. The percentages of subjects with categorical increases in SBP and DBP from baseline were lower in the PHEN/TPM groups than in the placebo group. The percentages of subjects with increases in heart rate >5, >10, and >15 bpm were lower in the placebo group than in the PHEN/TPM groups.

Table 45: Changes in Blood Pressure (mmHg) from baseline to Week 108 –2-year cohort (safety set)

	Placebo	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Number of subjects with baseline and endpoint measurements at Week 108	n=197	n=129	n=248
Systolic blood pressure (mmHg)			
Baseline mean (SD)	128.4 (14.45)	127.9 (11.71)	126.4 (13.61)
Week 108 mean change (SD)	-4.2 (15.12)	-5.0 (14.29)	-3.9 (14.00)
Comparison to placebo p-value		0.6276	0.7760
Diastolic blood pressure (mmHg)			
Baseline mean (SD)	79.7 (9.55)	79.8 (9.90)	79.5 (8.69)
Week 108 mean change (SD)	-3.6 (10.27)	-3.5 (9.62)	-2.9 (9.44)
Comparison to placebo p-value		0.9477	0.4861
Heart rate (bpm)			
Baseline mean (SD)	70.6 (10.25)	72.0 (9.56)	73.0 (10.27)
Week 108 mean change (SD)	0.4 (9.86)	1.3 (10.17)	1.7 (10.64)
Comparison to placebo p-value		0.4734	0.1771
Data from studies OB-303/305 Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303 Endpoint is the last available measurement obtained during the double-blind treatment period Source: Applicant's Table 3, Pg 12, CV risk assessment			

Table 46: Summary of categorical increases from baseline in blood pressure occurring at least once during the double-blind treatment period –2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
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	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 N (%)	PHEN/TPM 15/92 N=295 n (%)
Systolic blood pressure			
>5 mmHg	186 (81.9)	111 (72.5)	204 (69.2)
>10 mmHg	145 (63.9)	82 (53.6)	163 (55.3)
>15 mmHg	108 (47.6)	57 (37.3)	114 (38.6)
>20 mmHg	63 (27.8)	33 (21.6)	60 (20.3)
>25 mmHg	41 (18.1)	21 (13.7)	37 (12.5)
>30 mmHg	23 (10.1)	11 (7.2)	19 (6.4)
Diastolic blood pressure			
>5 mmHg	154 (67.8)	102 (66.7)	194 (65.8)
>10 mmHg	84 (37.0)	50 (32.7)	109 (36.9)
>15 mmHg	50 (22.0)	28 (18.3)	54 (18.3)
>20 mmHg	25 (11.0)	11 (7.2)	15 (5.1)
Heart rate			
>5 bpm	185 (81.5)	132 (86.3)	257 (87.1)
>10 bpm	127 (55.9)	97 (63.4)	211 (71.5)
>15 bpm	90 (39.6)	64 (41.8)	143 (48.5)
>20 bpm	49 (21.6)	26 (17.0)	76 (25.8)
Includes data from Studies OB-303 and OB-305 Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303 All measurements taken during the randomized, double-blind treatment period of OB-303/305 are considered Source: Applicant's Table 14.4.4.20, OB-305 CSR			

The rate pressure product (RPP), defined as the product of heart rate and SBP, has been shown to correlate with myocardial oxygen demand. The table below summarizes the change in RPP (divided by 100) from baseline to Week 108. The mean change in RPP from baseline was -2.2 for the placebo group, -2.0 for the mid-dose PHEN/TPM group and -0.6 for the high-dose PHEN/TPM group.

Table 47: Summary of rate-pressure product from baseline to Week 108 – 2-year cohort (safety set)

	Placebo (N=227)	PHEN/TPM 7.5/46 (N=153)	PHEN/TPM 15/92 (N=295)
n [1]	197	129	248
Baseline [2] mean (SD)	90.6 (16.11)	92.1 (14.85)	92.9 (16.08)
Week 108 mean (SD)	88.2 (15.63)	90.3 (15.66)	91.6 (14.93)
Mean change (SD)	-2.2 (17.15)	-2.0 (18.75)	-0.6 (16.19)
1. n is the number of subjects with measurements at both baseline and Week 108. 2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303. PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SD = standard deviation. Source: Post-text Table 14.4.4.24			

Further discussion of cardiovascular parameters is included in the Cardiovascular Risk Assessment section of this briefing document.

Highlights of PHEN/TPM safety

Table 48 lists side-by-side several safety endpoints from the 1-year and 2-year safety cohorts. The 1-year cohort is a larger cohort consisting of over 3,800 subjects from two 1 year trials (OB-302, OB-303), one 6-month study of subjects with type 2 diabetes (OB-202), and an additional 6-month double-blind extension period (DM-230). The 2-year safety cohort, OB-305, includes 675 subjects who started treatment in study OB-303 and were eligible at the end of OB-303 to continue in a 1-year double-blind extension period and therefore have a longer duration of PHEN/TPM exposure.

In general, there were a higher proportion of TEAEs, SAEs, and TMEs in the 2-year cohort which is not adjusted for duration of exposure. However, a lower proportion of subjects in the 2-year cohort discontinued due to an adverse event compared to the 1-year cohort.

Many of the TEAEs that occurred in $\geq 5\%$ of subjects in the 1-year cohort were also noted in the 2-year cohort; however, these cohorts are not mutually exclusive. Table 49 summarizes the TEAEs that occurred in $\geq 5\%$ in any treatment group for the 1-year and 2-year safety cohorts. The highlighted rows suggest a dose-response in frequency of adverse events with increasing PHEN/TPM doses. Paraesthesia, constipation, dry mouth, and dysgeusia were the TEAEs that increased in a dose-dependent manner in both the 1-year and 2-year safety cohorts. The preferred terms of insomnia and dizziness demonstrated a dose-response in the 1-year cohort and occurred in a higher proportion of PHEN/TPM-treated subjects compared to placebo-treated subjects in the 2-year cohort. Additional TEAEs with a $\geq 5\%$ occurrence and a dose-response only in the 2-year safety cohort included sinusitis, procedural pain, cough, fatigue, alopecia, and anxiety. It is important to note that in the 1-year cohort, the preferred terms of cough, anxiety, and alopecia were reported more frequently in the PHEN/TPM-exposed group compared to the placebo-exposed group, although with an incidence below 5%.

The measures of depression by PHQ-9 Question 9 and the composite score of suicidality from the C-SSRS in both cohorts were low and similar in frequency among treatment groups.

There were consistent patterns in both cohorts in regards to a dose-response in reductions in serum bicarbonate, with roughly 30% of individuals treated with high-dose PHEN/TPM compared to 4 to 6% in placebo groups, developing a bicarbonate of less than 21 mEq/L.

All treatment groups in both cohorts demonstrated a reduction in SBP and DBP from baseline. Of note, the treatment differences between placebo and PHEN/TPM groups were more pronounced in the 1-year cohort compared to the 2-year cohort. Increases in mean and categorical heart rate measurements were still evident after two years of treatment and were higher in high-dose PHEN/TPM compared to mid-dose PHEN/TPM treatment. An analysis of the RPP demonstrated a reduction in all treatment groups from baseline to Week 108. Treatment with placebo resulted in a numerically greater decrease in RPP compared to treatment with mid- and high-dose PHEN/TPM, however the difference between PHEN/TPM and placebo groups was small.

Conclusions regarding PHEN/TPM safety from study OB-305

The additional 52 weeks of safety data accrued with study OB-305 was consistent with the safety profile of PHEN/TPM from the 1-year safety cohort. The targeted medical events comprising psychiatric, cognitive, cardiac, and ophthalmic adverse events occurred in a higher proportion of PHEN/TPM-treated versus placebo-treated subjects. Low serum bicarbonate levels were present in a higher proportion of PHEN/TPM-treated subjects compared to placebo. Blood pressure was reduced from baseline across all treatment groups and heart rate increases with PHEN/TPM versus placebo treatment were evident after two years of treatment.

Table 48: 1-year and 2-year safety cohorts various assessments

	1-year safety cohort Week 56 (OB-202/DM-230, OB-302, OB-303)				2-year safety cohort Week 108 (OB-305)		
	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 (%)	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Completed all visits on study drug	857 (54.9)	138 (57.5)	344 (69.1)	1003 (63.5)	196 (86.3)	127 (82.5)	245 (83.1)
No drug holidays	1424 (91.2)	219 (91.3)	441 (88.6)	1393 (88.2)	189 (83.3)	124 (81.0)	235 (79.7)
Mean (SD) holiday duration (days)	28.9 (34.8)	36.2 (42.0)	27.2 (40.2)	24.7 (41.1)	17.9 (22.9)	26.1 (23.6)	23.3 (38.6)
Any change in dosing regimen	216 (13.8)	33 (13.8)	102 (20.5)	352 (22.3)	49 (21.6)	41 (26.8)	88 (29.8)
Deaths	1 (0.1)	0	0	0	0	0	0
Any treatment emergent SAE	52 (3.3)	6 (2.5)	14 (2.8)	57 (3.6)	14 (6.2)	9 (5.9)	24 (8.1)
SDAE	131 (8.4)	27 (11.3)	58 (11.6)	274 (17.3)	7 (3.1)	7 (4.6)	13 (4.4)
TEAE	1186 (76.0)	192 (80.0)	424 (85.1)	1377 (87.2)	218 (96.0)	142 (92.8)	277 (93.9)
Psychiatric TME	161 (10.3)	38 (15.8)	72 (14.5)	325 (20.6)	42 (18.5)	33 (21.6)	70 (23.7)
Cognitive TME	24 (1.5)	5 (2.1)	25 (5.0)	120 (7.6)	5 (2.2)	10 (6.5)	17 (5.8)
Cardiac TME	36 (2.3)	4 (1.7)	24 (4.8)	78 (4.9)	12 (5.3)	12 (7.8)	15 (5.1)
Ophthalmic TME	27 (1.7)	6 (2.5)	12 (2.4)	39 (2.5)	4 (1.8)	6 (3.9)	12 (4.1)
Positive PHQ-9	27 (1.7)	4 (1.7)	6 (1.2)	24 (1.5)	3 (1.3)	2 (1.3)	2 (0.7)
C-SSRS suicidality	11 (0.7)	1 (0.4)	3 (0.6)	14 (0.9)	3 (1.3)	1 (0.7)	2 (0.7)
Bicarbonate <21 mEq/L	92 (5.9)	39 (16.3)	112 (22.5)	474 (30.0)	9 (4.0)	35 (22.9)	90 (30.5)
SBP mean change from Baseline	-2.1	-3.3	-5.2	-5.2	-4.2	-5.0	-3.9
DBP mean change from Baseline	-1.9	-0.9	-3.3	-2.9	-3.6	-3.5	-2.9
HR mean change from Baseline	0	1.3	0.6	1.6	0.4	1.3	1.7
SBP >10 mmHg	733 (47.0)	101 (42.1)	182 (36.5)	645 (40.8)	145 (63.9)	82 (53.6)	163 (55.3)
DBP >15 mmHg	247 (15.8)	35 (14.6)	63 (12.7)	234 (14.8)	50 (22.0)	28 (18.3)	54 (18.3)
HR >10 bpm	657 (42.1)	120 (50.0)	251 (50.4)	887 (56.1)	127 (55.9)	97 (63.4)	211 (71.5)

Table 49: Summary of TEAE (≥5% in any treatment group by preferred term) – 1-year cohort (safety set); 2-year cohort (safety set)

	1-year safety cohort Week 56 (Studies OB-202/DM-230, OB-302, OB-303)				2-year safety cohort Week 108 Study OB-305			
Preferred term	Placebo N=1561 (%)	PHEN/TPM 3.75/23 N=240 (%)	PHEN/TPM 7.5/46 N=498 (%)	PHEN/TPM 15/92 N=1580 (%)	Preferred term	Placebo N=227 (%)	PHEN/TPM 7.5/46 N=153 (%)	PHEN/TPM 15/92 N=295 (%)
Paresthesia	1.9	4.2	13.7	19.9	URI	32.6	27.5	28.5
Dry mouth	2.8	6.7	13.5	19.1	Constipation	9.7	22.2	22.7
Constipation	6.1	7.9	15.1	16.1	Paresthesia	2.6	14.4	22.4
URI	12.8	15.8	12.2	13.5	Sinusitis	13.7	15.7	21.0
Headache	9.3	10.4	7.0	10.6	Dry mouth	2.6	14.4	20.7
Nasopharyngitis	8.0	12.5	10.6	9.4	Nasopharyngitis	22.0	19.0	17.3
Dysgeusia	1.1	1.3	7.4	9.4	Dysgeusia	1.8	11.8	13.6
Insomnia	4.7	5.0	5.8	9.4	Headache	11.5	7.2	12.9
Dizziness	3.4	2.9	7.2	8.6	Insomnia	9.7	12.4	11.5
Sinusitis	6.3	7.5	6.8	7.8	Influenza	8.4	13.7	10.5
Nausea	4.4	5.8	3.6	7.2	Procedural pain	4.4	9.2	9.5
Back pain	5.1	5.4	5.6	6.6	Influenza	8.4	13.7	10.5
Fatigue	4.3	5.0	4.4	5.9	Arthralgia	13.7	11.8	9.2
Diarrhea	4.9	5.0	6.4	5.6	Bronchitis	6.2	11.1	7.8
Blurred vision	3.5	6.3	4.0	5.4	Cough	3.1	7.2	7.8
Bronchitis	4.2	6.7	4.4	5.4	Nausea	7.0	8.5	7.5
UTI	3.6	3.3	5.2	5.2	Fatigue	5.7	5.9	7.1
Influenza	4.4	7.4	4.6	4.4	Dizziness	3.5	7.2	7.1
					Gastroenteritis	7.5	3.3	7.1
					Edema peripheral	5.7	2.0	6.1
					Gastroenteritis viral	6.2	7.2	5.8
					Alopecia	1.8	5.2	5.8
					Hypertension	6.6	3.3	5.8
					Pharyngolaryngeal pain	5.3	2.6	5.4
					Depression	5.3	2.6	5.4
					Seasonal allergy	4.8	3.9	5.4
					Blurred vision	4.4	3.3	5.1

1-year safety cohort Week 56 (Studies OB-202/DM-230, OB-302, OB-303)					2-year safety cohort Week 108 Study OB-305			
					Anxiety	3.1	3.9	5.1
					Pain in extremity	8.4	5.9	4.7
					Musculoskeletal pain	7.0	5.9	4.1
					Muscle spasms	5.7	3.9	4.1
					Osteoarthritis	3.5	5.2	4.1
					Muscle strain	3.5	5.2	4.1
					Sinus congestion	3.5	6.5	3.7
					Joint sprain	3.5	5.9	3.1
					Skin laceration	5.3	0	1.4
					Diabetes mellitus	5.3	2.6	1.4
Source: Table 11, 28; CR ISS, Pg 58, 93 In 2-year cohort, TEAE defined as adverse events that started on or after the first dose of double-blind study drug in study OB-303 and up to 28 days after the last dose of study drug in study OB-305								

V. Cardiovascular Risk Analysis

Relevant background information

The following information regarding the approval and withdrawal of the weight-loss drug Meridia® (sibutramine) was taken from FDA medical officer reviews of the subject matter.

Sibutramine (Meridia®) and SCOUT

Meridia® (sibutramine 5mg, 10mg, 15mg) was approved by FDA in 1997 for the management of obesity, including weight loss and maintenance of weight loss, in conjunction with a reduced calorie diet. Sibutramine was recommended for patients with an initial body mass index (BMI) $\geq 30 \text{ kg/m}^2$, or BMI $\geq 27 \text{ kg/m}^2$ with other risk factors (e.g., diabetes, high cholesterol, controlled high blood pressure). Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition.

During the initial review of the sibutramine application, it was determined that sibutramine satisfied one of the two efficacy criteria used by FDA to define efficacy – approximately 60% of sibutramine-treated subjects versus approximately 30% of placebo-treated subjects lost greater than 5% of baseline body weight. Sibutramine's adverse effects on systolic and diastolic blood pressure (mean increases of 1-3 mm Hg) and pulse (mean increases of 4-5 bpm) were identified as the primary safety concerns; however, the benefit-risk profile of 3 (5, 10, 15 mg) of the 5 (5, 10, 15, 20, 30 mg) proposed doses was deemed favorable and the blood pressure effects monitorable.

The initial European Union approval of sibutramine was in January 1999, but due to concerns about the potential long-term consequences of increases in blood pressure and pulse, a cardiovascular outcomes study was required as a post-approval commitment. This was the genesis of the Sibutramine Cardiovascular Outcomes (SCOUT) trial. Protocol development began in 2000.

SCOUT was a randomized, double-blind, placebo-controlled multicenter trial conducted between January 2003 and March 2009 in Europe, Latin America, and Australia. The study population consisted of approximately 10,000 men and women aged ≥ 55 with a body mass index (BMI) between 27 kg/m^2 and 45 kg/m^2 , or between 25 kg/m^2 and 27 kg/m^2 with an increased waist circumference. Participants were also required to have a history of cardiovascular disease (coronary artery disease, stroke, occlusive peripheral arterial disease) and/or type 2 diabetes mellitus with at least one other cardiovascular risk factor (i.e., hypertension, dyslipidemia, current smoking, or diabetic nephropathy). All participants underwent a 6-week lead-in period on sibutramine 10 mg. Eligible participants were then randomized to either placebo or sibutramine 10 mg daily. Titration to sibutramine 15 mg daily was allowed for subjects with inadequate weight loss on 10 mg daily. The mean duration of exposure to sibutramine and placebo was approximately 3.5 years.

There was a 16% increase in the relative risk of the primary outcome event (POE) (a composite of non-fatal MI, non-fatal stroke, resuscitation after cardiac arrest, and cardiovascular death) in the sibutramine group compared to the placebo group (HR, 1.16; 95% CI, 1.03, 1.31; $p=0.02$). There was no between-treatment difference in cardiovascular death (HR, 0.99; 95% CI, 0.82 to

1.19; $p=0.90$) or all-cause mortality (HR, 1.04; 95% CI, 0.91 to 1.20; $p=0.54$). The primary outcome was driven by non-fatal MI and non-fatal stroke (HR, 1.28; 95% CI, 1.04 to 1.57; $p=0.02$; HR, 1.36; 95% CI, 1.04 to 1.77; $p=0.03$, respectively).

The difference in mean percent body weight at Month 60 (end of trial) between the sibutramine and placebo groups was approximately 2.5%. Mean systolic and diastolic blood pressure and heart rate were consistently higher in the sibutramine-treated subjects throughout the randomization phase of the trial, with mean differences between the treatment groups ranging from -0.3 to 1.2 mm Hg systolic, 0.6 to 1.4 mm Hg diastolic, and 2.2 to 3.7 bpm.

An Advisory Committee meeting was held on September 15, 2010, to discuss the results of SCOUT. Eight of 16 committee members concluded that sibutramine should be withdrawn from the market because its CV risks outweigh the drug's benefits. Of the 8 committee members who voted to keep sibutramine on the market, 2 voted in favor of continued marketing with stronger warnings in labeling (to include a boxed warning), while 6 members voted for continued availability with stronger warnings in labeling and an upgraded REMS with elements to assure safe use, such as restricted distribution. Most committee members found the data did not support blood pressure or pulse monitoring as a clear way to mitigate the risk of a CV event. Many committee members said even though sibutramine reduces weight, there should be evidence of other accompanying benefit, such as CV benefit or improved glucose parameters.

After carefully evaluating the data, FDA was not able to identify a population for whom the benefits of the drug outweighed the risks. Since a population with a favorable benefit-risk profile could not be defined, FDA was not able to develop a risk mitigation strategy. It was the opinion of the Office of New Drugs and the Office of Surveillance and Epidemiology, that until or unless data are submitted showing a population that would clearly benefit from treatment with sibutramine, the drug should not remain on the market. On October 7, 2010, FDA asked Abbott Laboratories to voluntarily remove sibutramine from the U.S. market. The company complied.

PHEN/TPM Cardiovascular risk assessment

As part of the original NDA submission and the July 2010 EMDAC meeting, the observation of an increased heart rate in subjects treated with PHEN/TPM compared to placebo was reviewed and discussed. The EMDAC agreed that the observed increased heart rate was a significant concern especially over a long period of time. Therefore, one of the deficiencies cited in the CR letter concerned the cardiovascular safety of PHEN/TPM. In response to the CR letter, the applicant has provided the following:

- A summary of the changes observed regarding blood pressure, heart rate, and rate pressure product in the PHEN/TPM clinical development program, specifically in the:
 - One-year safety cohort ($n=3879$) overall and by baseline subgroups;
 - Two-year safety cohort ($n=675$); and
- A summary of heart rate measured via overnight polysomnogram in Study OB-204
- An analysis of heart rate outliers (defined as >10 bpm over baseline on two consecutive visits or heart rate >90 bpm on two consecutive visits) within the 1-year safety cohort

- Change in Cooper Clinic Mortality Risk Score and Framingham Risk Score
- Analysis of the occurrence of MACE within the PHEN/TPM clinical development program.

Four cohorts are referred to in this section and are defined as follows:

- **One-year safety cohort:** This cohort comprises all randomized subjects from studies OB-302, OB-303, and all subjects who entered study DM-230, the 6-month extension to study OB-202. Data for subjects in OB-202 and DM-230 were combined to provide 1-year safety data. Study OB-202 was a randomized, double-blind, placebo-controlled study of overweight and obese adults with type 2 diabetes. DM-230 was a 6 month extension of eligible subjects from study OB-202.
- **One-year completer population:** This cohort comprises all subjects from the 1-year studies OB-302 and OB-303 who completed all study visits on study drug.
- **Two-year safety cohort:** This cohort comprises all subjects who entered study OB-305, the 1-year extension study to OB-303. Data are presented for these subjects that summarizes the 2-year treatment period (OB-303 and OB-305).
- **Two-year completer population:** This cohort consists of all subjects who entered study OB-305, the 1-year extension study to OB-303 and completed all study visits on study drug. Data are presented for these subjects that summarizes the 2-year treatment period (OB-303 and OB-305).

The following tables outline the number and percentage of subjects in the 1-year safety cohort and 2-year safety cohort that had cardiovascular-related conditions at baseline.

Table 50: Percentage of subjects with cardiovascular-related medical conditions at baseline (1-year safety cohort)

Medical Condition	Placebo (N=1561) n (%)	QNEXA Low (N=240) n (%)	QNEXA Mid (N=498) n (%)	QNEXA Top (N=1580) n (%)
Dyslipidemia	399 (25.6)	5 (2.1)	180 (36.1)	416 (26.3)
Cardiovascular disease	228 (14.6)	5 (2.1)	74 (14.9)	255 (16.1)
Hypertension	627 (40.2)	33 (13.8)	261 (52.4)	642 (40.6)
Data from studies OB-202/DM-230, OB-302, and OB-303 are included. QNEXA=fixed-dose combination of phentermine and topiramate. QNEXA Low, 3.75/23 mg; QNEXA Mid, 7.5/46 mg; QNEXA Top, 15/92 mg.				

Cardiovascular disease: having either (1) a history of CAD, peripheral arterial occlusive disease, or stroke; or (2) diabetes plus 1 of the following: current smoker, hypertension, or dyslipidemia

Dyslipidemia: Using 2 medications for treatment of the condition at baseline or having a baseline triglyceride measurement at or above 200 mg/dL.

Hypertension: Using 2 medications for treatment of the condition at baseline or having a baseline SBP measurement between 140 and 160 mmHg (130-160 mmHg for diabetic subjects) or baseline DBP measurement between 90 and 100 mmHg (85-100 mmHg for diabetic subjects)

Table 51: Percentage of subjects with cardiovascular-related medical conditions at baseline (2-year safety cohort)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 n (%)	PHEN/TPM 15/92 N=295 n (%)
Hypertriglyceridemia	80 (35.2)	48 (31.4)	105 (35.6)
Cardiovascular disease	55 (24.2)	26 (17.0)	69 (23.4)

Hypertension	120 (52.9)	71 (46.4)	154 (52.2)
Source: Applicant's Supporting Table 14.1.2, pg 3, OB-305 CSR			

Mean Change in Blood Pressure and Heart Rate

One-year safety cohort

Table 52 summarizes mean changes in SBP, DBP, and heart rate in subjects with a baseline and study exit endpoint measurement. The mean SBP and DBP decreased in all treatment groups, but to a larger extent in the PHEN/TPM groups. Both the mid- and high-dose PHEN/TPM treatment groups had a statistically significant difference in mean blood pressure change compared to placebo. The mean change in SBP for mid- and high-dose groups was -5.2 mmHg versus -2.1 mmHg placebo, $p < 0.0001$. The mean change in DBP was numerically greater in the mid-dose PHEN/TPM treatment group compared to the high-dose PHEN/TPM treatment group (-3.3 mmHg and -2.9 mmHg, respectively). Both mid- and high-dose PHEN/TPM treatment groups had a statistically significant DBP treatment difference at Week 56 compared to placebo.

Mean heart rate was increased in all PHEN/TPM treatment groups compared to the placebo treatment group. High-dose PHEN/TPM-treated subjects had the largest mean treatment increase of 1.6 bpm compared to no change in the placebo-treated subjects.

Table 52: Mean changes in blood pressure and heart rate from baseline to endpoint – 1-year cohort (safety set)

	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Number of subjects 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)
Comparison to placebo p-value		0.2322	<0.0001	<0.0001
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)
Comparison to placebo p-value		0.1362	0.0044	0.0023
Heart rate (bpm)				
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)
Comparison to placebo p-value		0.0688	0.2933	<0.0001
Data from studies OB-202/DM-230, OB-302, and OB-303				
Baseline is the last measurement obtained on or before the first dose date of double-blind study drug				
Endpoint is the last available measurement obtained during the double-blind treatment period				
p-values obtained from ANOVA model with treatment as a fixed effect				
Source: Applicant's Table 1, Pg 10; Cardiovascular risk assessment report – CR submission				

The PHEN/TPM groups had a lower proportion of subjects with categorical increases in blood pressure compared to the placebo group (Table 53). However, PHEN/TPM-treated groups had a higher frequency of categorical increases in heart rate compared to the placebo-treated group. There were a higher proportion of high-dose PHEN/TPM-treated subjects with categorical increases in heart rate compared to mid-dose PHEN/TPM-treated subjects.

Table 53: Summary of categorical increase in blood pressure (mmHg) at any time 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 (%)
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)
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)
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 and blood pressure by baseline categories in 1-year safety cohort

Applicant-defined Baseline Cardiovascular Risk Categories

The applicant stratified subjects in the 1-year safety cohort into applicant-defined cardiovascular risk categories at baseline of high, medium, or low based on the following definitions:

High risk: Subjects with CV disease defined as

- History of coronary artery disease, peripheral arterial occlusive disease or stroke; or
- Has diabetes and one or both of the following conditions: hypertension or dyslipidemia

Moderate risk: Subjects with risk factors for CV disease

- Hypertension; or
- Dyslipidemia; or

▪ Diabetes mellitus

Low risk: Subjects with none of the above

Within the 1-year safety cohort there were 752 (19.8%) in the low-risk category, 2498 (65.6%) in the moderate-risk group, and 557 (14.6%) in the high-risk group. Within the subgroups, in general, PHEN/TPM-treated subjects experienced a greater mean decrease in blood pressure compared to placebo-treated subjects). Mean heart rate was generally higher in the PHEN/TPM-treated groups compared to the placebo-treated group within the subgroups of baseline cardiovascular risk. Within the highest baseline cardiovascular risk group, treatment with high-dose PHEN/TPM had the smallest placebo-subtracted mean increase in heart rate (0.5 bpm) compared to the medium baseline cardiovascular risk group (1.8 bpm) and low baseline cardiovascular risk group (2.0 bpm).

Table 54: Changes in BP and HR from baseline to Week 56 or study exit by baseline applicant-defined cardiovascular risk subgroups – 1-year cohort (safety set)

Parameter Subgroup	Statistic	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Change in systolic blood pressure (mmHg)					
Low baseline risk	n	281	114	30	327
	Mean (SD)	-0.2 (11.63)	-2.5 (11.74)	-4.9 (12.72)	-3.9 (11.99)
Medium baseline risk	n	1025	115	385	973
	Mean (SD)	-2.5 (14.58)	-3.6 (11.73)	-5.4 (14.45)	-5.7 (14.48)
High baseline risk	n	226	5	73	253
	Mean (SD)	-2.8 (13.96)	-15.4 (17.04)	-3.8 (17.15)	-5.2 (17.10)
Change in diastolic blood pressure (mmHg)					
Low baseline risk	n	281	114	30	327
	Mean (SD)	-0.1 (8.10)	0.1 (8.76)	-2.6 (7.51)	-2.0 (8.64)
Medium baseline risk	n	1025	115	385	973
	Mean (SD)	-2.3 (9.93)	-1.7 (7.76)	-3.4 (9.89)	-3.3 (9.53)
High baseline risk	n	226	5	73	253
	Mean (SD)	-2.4 (9.68)	-6.6 (5.27)	-3.3 (10.65)	-2.9 (9.78)
Change in heart rate (bpm)					
Low baseline risk	n	281	114	30	327
	Mean (SD)	-0.3 (10.27)	1.9 (10.63)	1.7 (8.58)	1.7 (9.81)
Medium baseline risk	n	1025	115	385	973
	Mean (SD)	-0.1 (10.16)	0.8 (10.23)	0.5 (10.27)	1.7 (10.57)
High baseline risk	n	226	5	73	253
	Mean (SD)	0.7 (10.21)	0.6 (3.13)	0.5 (10.40)	1.2 (9.73)
<p>1. n is the number of subjects with measurements at both baseline and Week 108.</p> <p>2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303.</p> <p>PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SD = standard deviation.</p> <p>Source: Supporting Post-text Tables 40, 41, and 42</p>					

Source: Applicant's PHEN/TPM CV risk assessment – CR submission

By baseline heart rate

The applicant analyzed the changes in heart rate by baseline heart rate by the following categories: mean baseline heart rate <60 bpm, 60 to 90 bpm, and >90 bpm. The analyses showed that those with the lowest baseline heart rate experienced the greatest increase in heart rate (Table 55) from baseline to Week 56/Early Termination. Of the 150 subjects with a baseline heart rate >90 bpm, heart rate declined across all treatment groups, however to a slightly lesser extent in the mid- and high-dose PHEN/TPM groups compared to the placebo group. It is still

notable that in the majority of subjects treated with high-dose PHEN/TPM in this analysis (i.e., subjects with heart rate ≤ 90 bpm) there was a 1.6 to 1.8 bpm increase over placebo.

Table 55: Changes in heart rate from baseline to Week 56/Early termination by baseline heart rate subgroups – 1-year cohort (safety set)

Parameter Subgroup	Statistic	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Change in heart rate (bpm)					
Baseline heart rate <60 bpm	n	96	12	27	107
	Mean (SD)	7.5 (10.39)	12.6 (13.52)	6.2 (6.15)	9.3 (8.89)
Baseline heart rate ≥ 60 bpm to ≤ 90 bpm	n	1378	215	438	1384
	Mean (SD)	0.1 (9.49)	1.2 (9.50)	0.9 (9.68)	1.7 (9.70)
Baseline heart rate >90 bpm	n	58	7	23	62
	Mean (SD)	-13.7 (12.13)	-14.4 (6.29)	-12.6 (12.85)	-11.9 (11.40)
1. n is the number of subjects with measurements at both baseline and Week 108. 2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303. PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SD = standard deviation. Source: Supporting Post-text Table 43					

Source: Applicant's CV risk assessment report – CR submission

By additional subgroups of interest

Further subgroups were defined to analyze the mean change in vital signs within the 1-year safety cohort. The following subgroups (presence of hypertension, use of beta blockers, and amount of weight loss) are highlighted in the text and table below.

Subjects with hypertension experienced a greater decrease in systolic and diastolic blood pressure compared to the corresponding treatment groups of subjects without hypertension. Mean heart rate was higher in the mid- and high-dose PHEN/TPM treatment groups in both hypertensive subgroups compared to placebo (HTN subgroup mid-dose PHEN/TPM +0.9 bpm, high-dose PHEN/TPM +1.0 bpm over placebo, no HTN subgroup mid-dose PHEN/TPM +0.1 bpm, high-dose PHEN/TPM +2.0 bpm).

Among subjects with and without concomitant beta blocker use, similar decreases in systolic and diastolic blood pressure were noted. There was some evidence that subjects not on beta blockers had numerically higher increases in heart rate compared to those with beta blocker use.

In the subgroups defined by the amount of weight change (no weight loss/weight gain, 0 to <5% weight loss, ≥ 5 to <10% weight loss, $\geq 10\%$ weight loss), the group with no weight loss/weight gain and therefore no presumed benefit with PHEN/TPM treatment still experienced a decrease in SBP and DBP which may be related to topiramate's general effect on blood pressure, although as expected, these subjects did not experience as great a decrease in SBP and DBP as those with larger amounts of weight loss.

For each weight change category, the PHEN/TPM-treated subjects had a higher increase in mean heart rate compared to placebo-treated subjects from baseline to Week 56. Of note, in the subgroup that gained or failed to lose weight there was a mean heart rate increase over placebo of 1.5 bpm, 0.1 bpm, and 0.4 bpm in the low-, mid-, and high-dose PHEN/TPM groups, respectively, at Week 56. In subjects who lost $\geq 10\%$ of their baseline weight, the placebo-treated group had a mean heart rate decrease of -4.0 bpm compared to a -1.5 bpm decrease in the

low-dose PHEN/TPM group, -0.5 bpm decrease in the mid-dose PHEN/TPM group, and +2.1 bpm increase in the high-dose PHEN/TPM group.

Table 56: Mean change in blood pressure and heart rate by subgroups Week 56 – 1 year cohort (safety set)

Parameter Subgroup	Statistic	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Change in SBP					
HTN	n	617	33	256	634
	Mean (SD)	-5.5 (15.3)	-5.8 (17.3)	-7.0 (16.2)	-8.5 (16.1)
No HTN	n	915	201	232	919
	Mean (SD)	0.1 (12.6)	-2.9 (10.8)	-3.1 (12.7)	-3.0 (12.8)
Beta blockers	n	219	13	95	212
	Mean (SD)	-2.2 (17.0)	-3.4 (10.4)	-3.3 (16.5)	-5.1 (16.2)
No beta blockers	n	1313	221	393	1341
	Mean (SD)	-2.1 (13.5)	-3.3 (12.1)	-5.6 (14.3)	-5.2 (14.2)
No wt loss/gain	n	618	48	59	135
	Mean (SD)	-0.1 (13.7)	0 (13.1)	-1.2 (19.0)	-0.4 (14.5)
0 to <5%	n	610	81	126	351
	Mean (SD)	-2.4 (13.3)	-3.7 (9.4)	-2.7 (12.7)	-2.8 (13.9)
≥5 to <10%	n	189	61	121	337
	Mean (SD)	-4.7 (14.3)	-6.4 (12.4)	-3.3 (15.5)	-5.2 (14.0)
≥ 10%	n	114	44	182	730
	Mean (SD)	-8.2 (16.1)	-2.0 (13.4)	-9.4 (13.1)	-7.2 (14.6)
Change in DBP					
HTN	n	617	33	256	634
	Mean (SD)	-3.9 (10.4)	-2.3 (9.9)	-5.0 (10.1)	-5.3 (9.6)
No HTN	n	915	201	232	919
	Mean (SD)	-0.6 (8.8)	-0.7 (8.0)	-1.4 (9.3)	-1.3 (8.9)
Beta blockers	n	219	13	95	212
	Mean (SD)	-2.1 (11.0)	-4.2 (8.6)	-2.5 (9.7)	-4.2 (10.4)
No beta blockers	n	1313	221	393	1341
	Mean (SD)	-1.9 (9.4)	-0.7 (8.3)	-3.5 (9.9)	-2.7 (9.2)
No wt loss/gain	n	618	48	59	135
	Mean (SD)	-0.7 (9.5)	1.4 (8.0)	-1.2 (10.8)	-2.0 (9.4)
0 to <5%	n	610	81	126	351
	Mean (SD)	-1.6 (9.5)	-1.7 (8.0)	-0.5 (8.9)	-1.2 (9.3)
≥5 to <10%	n	189	61	121	337
	Mean (SD)	-4.4 (8.8)	-2.7 (9.4)	-3.4 (10.5)	-3.2 (9.5)
≥ 10%	n	114	44	182	730
	Mean (SD)	-6.1 (10.4)	0.5 (7.0)	-5.9 (9.1)	-3.9 (9.3)
Change in HR					
HTN	n	617	33	256	634
	Mean (SD)	0.1 (10.2)	-0.7 (10.2)	1.0 (10.1)	1.1 (10.4)
No HTN	n	915	201	232	919
	Mean (SD)	0 (10.2)	1.6 (10.3)	0.1 (10.3)	2.0 (10.2)
Beta blockers	n	219	13	95	212
	Mean (SD)	-0.2 (10.2)	-0.4 (11.1)	0 (11.1)	1.9 (10.3)
No beta blockers	n	1313	221	393	1341
	Mean (SD)	0 (10.2)	1.4 (10.3)	0.7 (10.0)	1.6 (10.3)
No wt loss/gain	n	618	48	59	135
	Mean (SD)	0.7 (9.7)	2.2 (9.3)	0.8 (9.7)	1.1 (10.6)

Parameter Subgroup	Statistic	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
0 to <5%	n Mean (SD)	610 0 (10.4)	81 3.2 (11.3)	126 1.0 (9.6)	351 1.6 (9.5)
≥5 to <10%	n Mean (SD)	189 0.1 (10.6)	61 0.2 (10.0)	121 1.5 (11.0)	337 0.8 (10.2)
≥ 10%	n Mean (SD)	114 -4.0 (10.3)	44 -1.5 (9.4)	182 -0.5 (10.1)	730 2.1 (10.6)

Blood pressure and heart rate changes in the completer population at 1-year

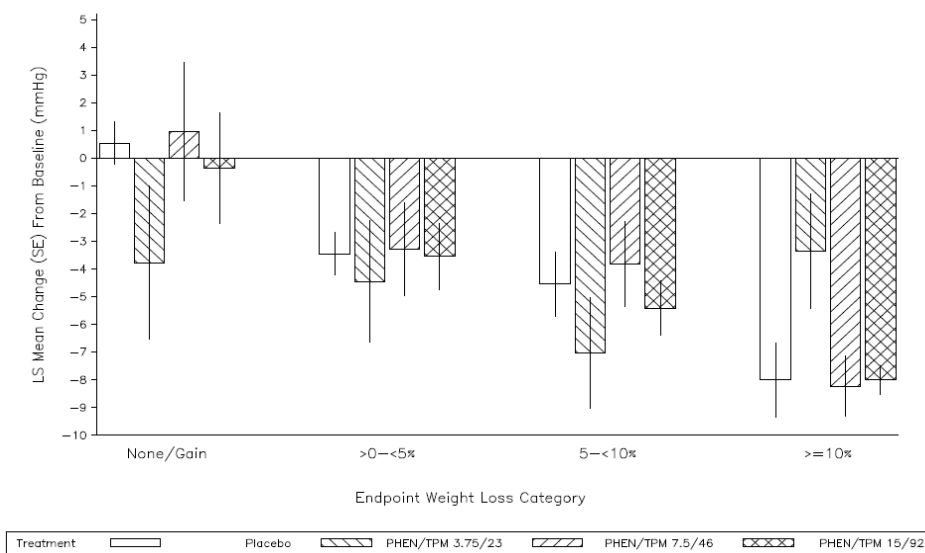
The applicant was asked to submit the vital sign changes by weight change category in subjects completing all visits on study drug in studies OB-302 and OB-303. Of the 3,678 subjects in the combined ITT set for studies OB-302 and OB-303 there were 2,222 subjects (60.4%) who completed the studies on study drug. The table below breaks down the number of completers in each weight change category.

Table 57: Number (%) of completers by weight loss category at Week 56 (completer population)

	Placebo N=805	PHEN/TPM 3.75/23 N=138	PHEN/TPM 7.5/46 N=344	PHEN/TPM 15/92 N=935
No change/gain	307 (38.1)	23 (16.7)	28 (8.1)	41 (4.4)
>0 to <5%	287 (35.7)	33 (23.9)	61(17.7)	103 (11.0)
≥5 to <10%	125 (15.5)	44 (31.9)	87 (25.3)	180 (19.3)
≥ 10%	86 (10.7)	38 (27.5)	168 (48.8)	611 (65.3)
Source: Derived from IR submitted 1/11/12 submission 0066 Data includes study OB-302 and OB-303				

The bar graphs below shows the changes from baseline to Week 56 for SBP for each weight response category in the 1-year completer population (Figure 4). With the exception of the mid-dose PHEN/TPM treatment group in the no weight loss category, all PHEN/TPM treatment groups experienced a reduction in SBP. There were no statistically significant differences in SBP between PHEN/TPM and placebo treatment groups.

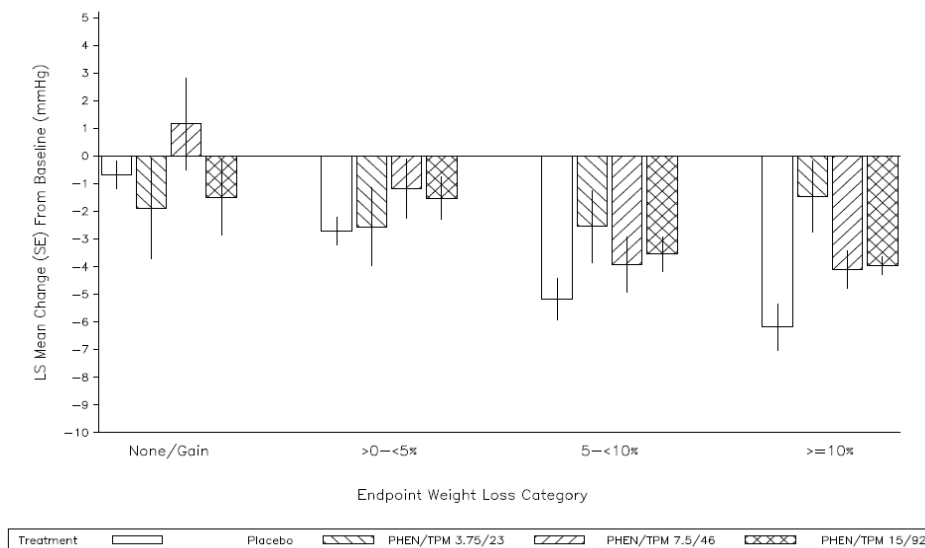
Figure 4: Change in SBP at Week 56 by body weight change – 1-year completer population



Source: Applicant's Figure IR response submitted 1/11/12 submission 0066

Changes in DBP by weight loss category in the completer population are depicted in the bar graphs below (Figure 5). Again with the exception of mid-dose PHEN/TPM treatment in the no weight loss group, all PHEN/TPM groups demonstrated a reduction in DBP. In subjects with weight loss, the reduction in DBP was numerically larger with placebo compared to PHEN/TPM.

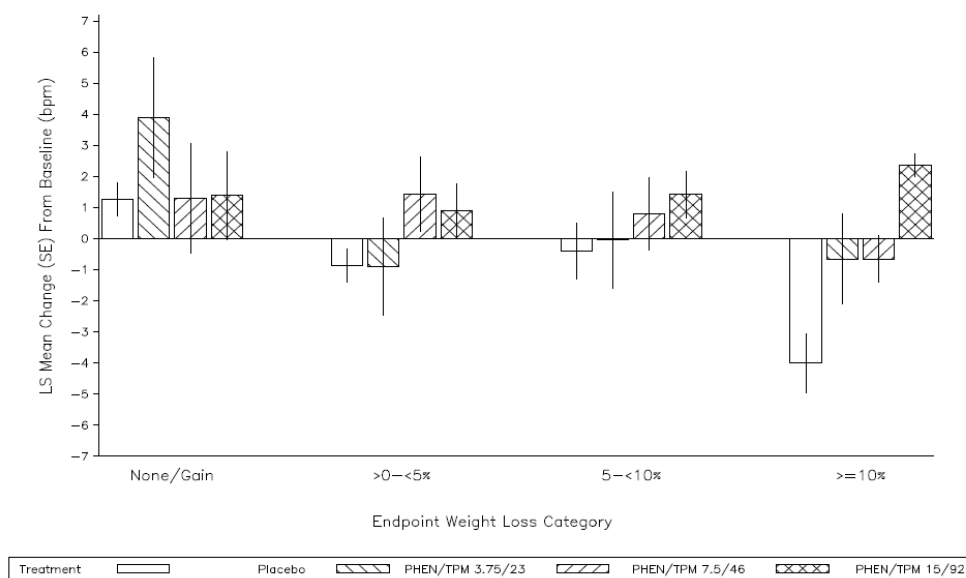
Figure 5: Change in DBP at Week 56 by body weight change – 1-year completer population



Source: Applicant's Figure IR response submitted 1/11/12 submission 0066

The bar graphs below depict the heart rate change in completers after 1 year of treatment (Figure 6). In the group that did not lose weight, heart rate increased in all treatment groups, with the greatest increase (LS mean 3.9 bpm) in the low-dose PHEN/TPM group. Mid- and high-dose PHEN/TPM treatment had a similar increase in heart rate compared to placebo treatment. The largest treatment difference occurred in the group that lost 10% of weight from baseline. There was a LS mean heart rate difference of 3.3 bpm between the mid-dose PHEN/TPM group ($p=0.0045$) and the placebo group and 6.4 bpm between the high-dose PHEN/TPM group and the placebo group ($p < 0.0001$).

Figure 6: Change in heart rate at Week 56 by body weight change – 1-year completer population



Source: Applicant's Figure IR response submitted 1/11/12 submission 0066

Two-year safety cohort

The 2-year safety cohort consists of 675 subjects who completed study OB-303 and were eligible and elected to participate in study OB-305, the 1-year extension of study OB-303. Analyzing subjects with a baseline (start of OB-303) and Week 108 measurement, a decrease in SBP and DBP was observed across all treatment groups (Table 58). However, there were no statistically significant blood pressure treatment differences between the PHEN/TPM-treated subjects and placebo-treated subjects (mean placebo difference of SBP -0.8 mmHg at mid-dose, $p=0.6$; and +0.3 mmHg at high-dose; $p=0.8$). These results are in contrast to the findings in the 1-year safety cohort, which was made up of additional subjects from study OB-202, study DM-230, OB-302, and OB-303, which demonstrated a statistical improvement in blood pressure with PHEN/TPM treatment compared to placebo treatment (mean placebo difference of SBP ~3.1 mmHg at mid- and high-dose PHEN/TPM, $p < 0.0001$ for both).

The mean heart rate increased in all treatment groups in the 2-year cohort, but larger mean increases in the PHEN/TPM treated groups were observed (0.9 bpm and 1.3 bpm, mid- and high-

dose PHEN/TPM, over placebo respectively). None of the between-treatment group differences achieved statistical significance.

Consistent with the 1-year safety cohort, subjects treated with placebo had more categorical increases in SBP and DBP compared to subjects treated with PHEN/TPM. As expected, more subjects treated with placebo had less categorical increases in heart rate compared to subjects treated with PHEN/TPM. The high-dose PHEN/TPM group had larger proportions of heart rate categorical increases compared to the mid-dose PHEN/TPM and placebo groups.

Table 58: Changes in blood pressure and heart rate from baseline to Week 108 – 2-year cohort (safety set)

	Placebo	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Number of subjects with baseline and endpoint measurements at Week 108	n=197	n=129	n=248
Systolic blood pressure (mmHg)			
Baseline mean (SD)	128.4 (14.45)	127.9 (11.71)	126.4 (13.61)
Week 108 mean change (SD)	-4.2 (15.12)	-5.0 (14.29)	-3.9 (14.00)
Comparison to placebo p-value		0.6276	0.7760
Diastolic blood pressure (mmHg)			
Baseline mean (SD)	79.7 (9.55)	79.8 (9.90)	79.5 (8.69)
Week 108 mean change (SD)	-3.6 (10.27)	-3.5 (9.62)	-2.9 (9.44)
Comparison to placebo p-value		0.9477	0.4861
Heart rate (bpm)			
Baseline mean (SD)	70.6 (10.25)	72.2 (9.67)	73.0 (10.27)
Week 108 mean change (SD)	0.4 (9.86)	1.3 (10.17)	1.7 (10.64)
Comparison to placebo p-value		0.4734	0.1771
Data from studies OB-303/305 Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303 Endpoint is the last available measurement obtained during the double-blind treatment period p-values obtained from ANOVA model with treatment as a fixed effect Source: Applicant's Table 3, Pg 12, CV risk assessment – CR submission 17 Oct 2011			

Table 59: Summary of categorical increases from baseline in blood pressure – 2-year cohort (safety set)

	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 N (%)	PHEN/TPM 15/92 N=295 n (%)
Systolic blood pressure			
>5 mmHg	186 (81.9)	111 (72.5)	204 (69.2)
>10 mmHg	145 (63.9)	82 (53.6)	163 (55.3)
>15 mmHg	108 (47.6)	57 (37.3)	114 (38.6)
>20 mmHg	63 (27.8)	33 (21.6)	60 (20.3)
>25 mmHg	41 (18.1)	21 (13.7)	37 (12.5)
>30 mmHg	23 (10.1)	11 (7.2)	19 (6.4)
Diastolic blood pressure			
>5 mmHg	154 (67.8)	102 (66.7)	194 (65.8)
>10 mmHg	84 (37.0)	50 (32.7)	109 (36.9)

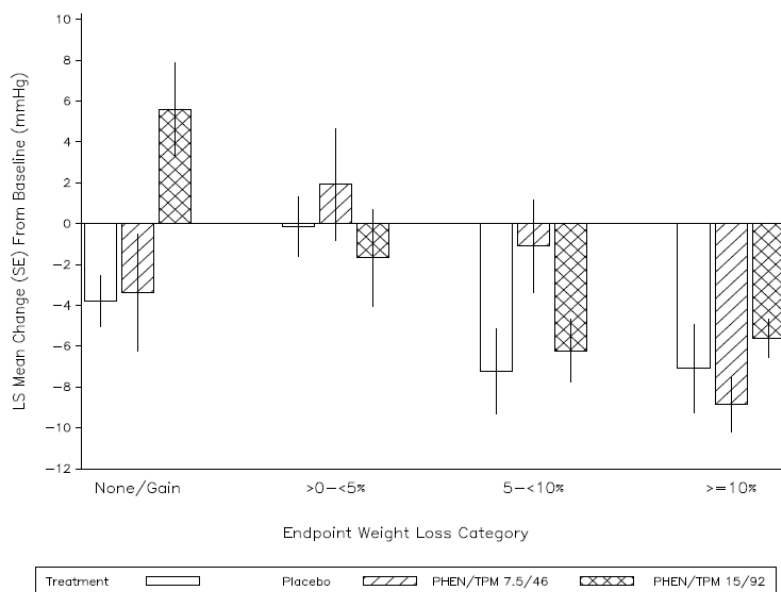
	Placebo N=227 n (%)	PHEN/TPM 7.5/46 N=153 N (%)	PHEN/TPM 15/92 N=295 n (%)
>15 mmHg	50 (22.0)	28 (18.3)	54 (18.3)
>20 mmHg	25 (11.0)	11 (7.2)	15 (5.1)
Heart rate			
>5 bpm	185 (81.5)	132 (86.3)	257 (87.1)
>10 bpm	127 (55.9)	97 (63.4)	211 (71.5)
>15 bpm	90 (39.6)	64 (41.8)	143 (48.5)
>20 bpm	49 (21.6)	26 (17.0)	76 (25.8)
Includes data from Studies OB-303 and OB-305 Baseline is the last measurement obtained on or before the first dose date of double-blind study drug in study OB-303 All measurements taken during the randomized, double-blind treatment period of OB-303/305 are considered Source: Applicant's Table 14.4.4.20, OB-305 CSR			

Blood pressure and heart rate changes in the completer population at two years

Of the 675 subjects in the two year ITT set, 568 (84.1%) completed all study visits on study drug. The applicant submitted the blood pressure and heart rate changes by weight change categories in this completer population, which are depicted in the bar graphs below.

Consistent reductions in SBP with PHEN/TPM treatment were noted with $\geq 5\%$ weight loss (Figure 7). In general reductions in SBP with PHEN/TPM were numerically smaller than that observed with placebo treatment with the exception of mid-dose PHEN/TPM treatment in subjects with $\geq 10\%$ weight loss.

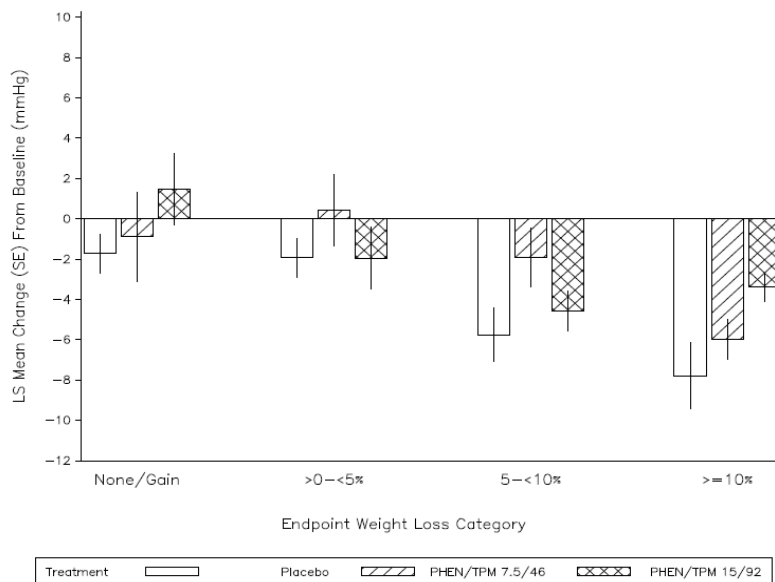
Figure 7: Change in SBP at Week 108 from baseline – 2-year completer population



Source: Applicant's Figure IR response submitted 1/11/12 submission 0066

Treatment with placebo resulted in numerically larger reductions in DBP compared to PHEN/TPM treatment (Figure 8). Consistent decreases in DBP were noted with in subjects treated with PHEN/TPM with $\geq 5\%$ weight loss.

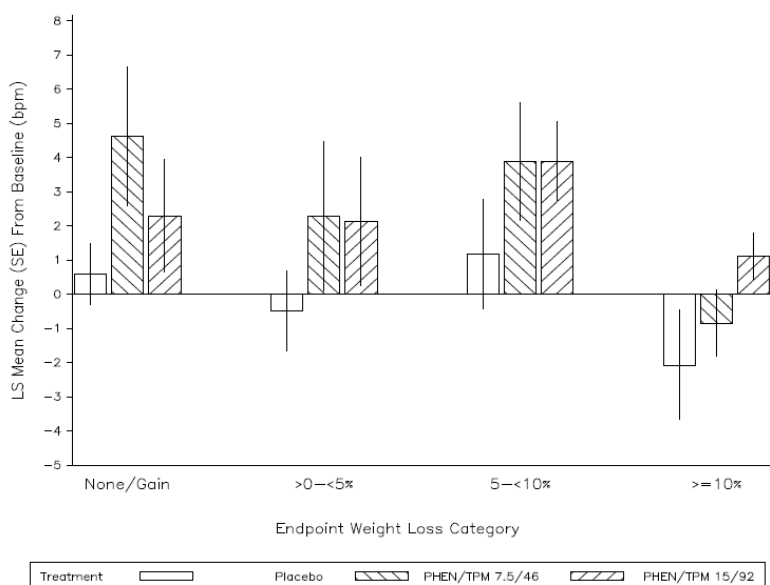
Figure 8: Change in DBP at Week 108 from baseline – 2-year completer population



Source: Applicant's Figure IR response submitted 1/11/12 submission 0066

The bar graphs below depict the change in heart rate at Week 108 in the 2-year completer population (Figure 9). In the group without weight loss, treatment with placebo, mid- and high-dose PHEN/TPM increased heart rate by 0.6 bpm, 4.6 bpm and 2.3 bpm, respectively. Across increasing amounts of weight loss, the LS mean heart rate treatment differences between PHEN/TPM and placebo groups persisted.

Figure 9: Change in heart rate at Week 108 from baseline – 2-year completer population



Source: Applicant's Figure IR response submitted 1/11/12 submission 0066

Study OB-204

Study OB-204 was a Phase 2 study in 45 obese adults with obstructive sleep apnea (OSA). After a baseline overnight polysomnogram (PSG), subjects with moderate-to-severe OSA were randomized to high-dose PHEN/TPM or placebo for a 28-week treatment period. Follow-up overnight PSG tests were done at 8 and 28 weeks. On the PSG visit, vital signs were obtained before and after the test. During the overnight PSG, heart rate was continuously recorded and averaged over 8 hours.

By Week 28 (with LOCF) the LS mean percent change in weight from baseline was -4.21% in the placebo group and -10.26% in the high-dose PHEN/TPM group ($p=0.0006$ compared to placebo). Seventy-three percent of high-dose PHEN/TPM treated subjects achieved at least 5% weight loss compared to 47.8% in the placebo group, the comparison however did not achieve nominal statistical significance ($p=0.08$). However, 54.5% of high-dose PHEN/TPM-treated subjects lost at least 10% of baseline weight compared to 13.0% of placebo-treated-subjects ($p=0.004$ compared to placebo).

The PSG data showed that the mean overnight heart rate at Week 28 was reduced by 3.3 bpm in the placebo group and 4.8 bpm in the high-dose PHEN/TPM group compared to their respective baseline values (Table 60). The difference between the placebo and high-dose PHEN/TPM group was not statistically significant.

Manual measurements of heart rate were obtained in study OB-204 at every study visit. The PHEN/TPM-treated group experienced a LS mean increase in heart rate of 7.7 bpm compared to a 1.7 bpm increase in the placebo-treated group ($p = 0.07$) after 28 weeks of treatment (Table 61).

Table 60: Mean overnight heart rate during polysomnography – Study OB-204

	Placebo N=21		PHEN/TPM 15/92 N=19	
	Baseline	Week 28	Baseline	Week 28
Mean overnight heart rate (bpm) by PSG averaged over 8 hours	68.1	64.8	71.6	66.9

Table 61: Change in blood pressure and heart rate from baseline to Week 8 and Week 28 with LOCF

Time Point Parameter	LS Mean (SE)		p-value
	Placebo	VI-0521	
Week 8	(n=21)	(n=21)	
Systolic Blood Pressure (mm Hg)	-9.4 (3.18)	-11.2 (3.18)	0.6829
Diastolic Blood Pressure (mm Hg)	-7.2 (1.81)	-2.4 (1.81)	0.0707
Heart Rate (bpm)	1.0 (2.86)	6.0 (2.86)	0.2348
Week 28 with LOCF [1]	(n=23)	(n=22)	
Systolic Blood Pressure (mm Hg)	-7.3 (2.58)	-15.0 (2.63)	0.0431
Diastolic Blood Pressure (mm Hg)	-5.6 (1.86)	-6.3 (1.90)	0.7991
Heart Rate (bpm)	1.7 (2.26)	7.7 (2.31)	0.0708

Source: [Section 14.2](#), [Table 33](#), [Table 35](#), and [Table 37](#)

LS mean, SE, 95% CI, and p-value are obtained from an ANCOVA model with treatment as fixed effects and baseline body weight as a covariate.

[1] Week 28 with LOCF is defined as the last available measurement during the double-blind treatment period.

Any conclusions regarding these results from the overnight polysomnogram testing are limited and do not necessarily suggest a profile of reduced risk of cardiovascular events with PHEN/TPM use. While it is true that a blunted nocturnal dip in blood pressure and heart rate are associated with increased cardiovascular adverse events, these data have been primarily obtained from ambulatory blood pressure monitoring over a 24-hour period to document the patterns of blood pressure and heart rate. There is also evidence to suggest that in hypertensive conditions that result in loss of nocturnal blood pressure reduction, nocturnal bradycardia is partially preserved, and therefore, one would need blood pressure to confirm a uniformly normal night-time dip.³

Heart rate outliers

Mean change in blood pressure and heart rate by heart rate outlier status

Subjects in the 1-year safety cohort with heart rate elevations were defined as having an increase in heart rate >10 bpm over baseline at two or more consecutive visits or having a heart rate >90

³ Portaluppi, F et al. Circadian rhythms and cardiovascular health. Sleep Medicine Reviews. 2011: 1-16

bpm at two or more consecutive visits during the double-blind treatment period. Of the 3,807 subjects with blood pressure and heart rate measurements at baseline and Week 56 or study exit, there were a higher proportion of PHEN/TPM-treated subjects who met the definition of having a heart rate elevation compared to placebo-treated subjects.

Mean SBP decreased in both heart rate subgroups with PHEN/TPM-treated subjects experiencing similar or larger mean reductions in SBP compared to placebo-treated subjects (Table 62). Between subgroup comparisons of corresponding treatment groups showed larger mean SBP reductions in non-heart rate outliers except for the high-dose PHEN/TPM treatment group.

Mean DBP decreased in nearly all treatment groups for both heart rate subgroups, with larger reductions observed in the mid- and high-dose PHEN/TPM groups compared to placebo group in both subgroups.

As expected there were larger increases in mean heart rate in heart rate outliers compared to non-heart rate outliers. Within the heart rate outlier subgroup, only treatment with high-dose PHEN/TPM resulted in a mean increase over placebo (+0.4 bpm).

Table 62: Change in heart rate from baseline to Week 56/Early Termination – Heart rate elevation subgroups – 1-year cohort (safety set)

Parameter Subgroup Statistic	Placebo	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92
Systolic Blood Pressure (mmHg)				
With Heart Rate Elevations				
n [1]	284	65	132	488
Baseline [2] mean (SD)	126.7 (13.13)	122.0 (11.71)	129.1 (14.47)	125.3 (13.14)
Endpoint [3] mean (SD)	124.3 (12.92)	119.5 (12.85)	124.8 (14.17)	118.7 (13.14)
Mean change (SD)	-2.5 (14.88)	-2.5 (12.96)	-4.3 (16.32)	-6.6 (14.43)
Median (Min, Max) change	-2.0 (-39, 46)	-4.0 (-36, 46)	-4.0 (-42, 64)	-6.0 (-49, 35)
Without Heart Rate Elevations				
n [1]	1248	169	356	1065
Baseline [2] mean (SD)	126.4 (13.28)	122.7 (10.90)	128.3 (13.32)	125.9 (13.11)
Endpoint [3] mean (SD)	124.4 (13.80)	119.0 (12.04)	122.9 (14.04)	121.3 (13.58)
Mean change (SD)	-2.1 (13.81)	-3.6 (11.56)	-5.5 (14.16)	-4.6 (14.46)
Median (Min, Max) change	-2.0 (-59, 46)	-4.0 (-44, 41)	-5.5 (-45, 36)	-4.0 (-76, 53)
Diastolic Blood Pressure (mmHg)				
With Heart Rate Elevations				
n [1]	284	65	132	488
Baseline [2] mean (SD)	80.0 (9.11)	76.3 (8.00)	81.0 (9.47)	78.9 (8.73)
Endpoint [3] mean (SD)	78.0 (9.66)	77.1 (8.28)	77.8 (9.53)	75.6 (8.81)
Mean change (SD)	-2.0 (9.99)	0.9 (8.25)	-3.2 (11.05)	-3.3 (9.58)
Median (Min, Max) change	-2.0 (-37, 30)	1.0 (-16, 18)	-4.0 (-32, 38)	-4.0 (-31, 26)
Without Heart Rate Elevations				
n [1]	1248	169	356	1065
Baseline [2] mean (SD)	79.5 (8.91)	78.4 (7.22)	80.5 (8.42)	79.1 (8.77)
Endpoint [3] mean (SD)	77.7 (9.61)	76.8 (8.25)	77.2 (8.56)	76.3 (8.81)
Mean change (SD)	-1.9 (9.53)	-1.6 (8.22)	-3.4 (9.41)	-2.8 (9.32)
Median (Min, Max) change	-2.0 (-53, 34)	-1.0 (-20, 28)	-3.0 (-30, 29)	-3.0 (-31, 30)
Heart rate (bpm)				
With Heart Rate Elevations				
n [1]	284	65	132	488
Baseline [2] mean (SD)	69.2 (11.05)	68.6 (9.81)	69.7 (11.63)	70.0 (11.06)
Endpoint [3] mean (SD)	77.0 (12.41)	76.4 (10.90)	75.7 (11.43)	78.2 (10.75)
Mean change (SD)	7.9 (9.94)	7.9 (10.33)	6.1 (11.74)	8.3 (9.50)
Median (Min, Max) change	8.0 (-16, 59)	6.0 (-14, 46)	7.0 (-42, 38)	8.0 (-30, 35)
Without Heart Rate Elevations				
n [1]	1248	169	356	1065
Baseline [2] mean (SD)	73.2 (9.05)	73.7 (8.58)	73.1 (9.28)	73.9 (9.00)
Endpoint [3] mean (SD)	71.4 (9.13)	72.5 (9.04)	71.6 (9.68)	72.5 (8.83)
Mean change (SD)	-1.8 (9.37)	-1.2 (9.16)	-1.5 (8.72)	-1.4 (9.14)
Median (Min, Max) change	-2.0 (-51, 40)	0.0 (-26, 26)	-1.0 (-40, 22)	-1.0 (-34, 30)
Data from studies OB-202/DM-230, OB-302, and OB-303 are included.				
1. n is the number of subjects with baseline and endpoint measurements.				
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.				
3. Endpoint is the last available measurement obtained during the double-blind treatment period.				
ET = early termination; PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SD = standard deviation.				
Source: Supporting Post-text Tables 24 and 25				

Adverse events by heart rate elevation outlier status

There were a slightly higher proportion of heart rate outliers with a TEAE in the mid- and high-dose PHEN/TPM groups compared to the corresponding treatment group of non-heart rate outliers (Table 63). For each treatment group, the incidences of AEs resulting in study drug discontinuation were higher in non-heart rate outliers compared to heart rate outliers. Treatment-emergent SAEs occurred with a higher proportion in non-heart rate outliers compared to heart-rate outliers except for the mid-dose PHEN/TPM treatment group. Overall, no specific treatment-emergent SAE occurred in more than 2 subjects.

Table 63: Overview of adverse events in heart rate outliers and non-heart rate outliers – 1-year cohort (safety set)

	With heart rate elevations				Without heart rate elevations			
	Placebo N=284 n (%)	PHEN/TP M 3.75/23 N=65 n (%)	PHEN/TPM 7.5/46 N=132 n (%)	PHEN/TPM 15/92 N=488 n (%)	Placebo N=1277 n (%)	PHEN/TPM 3.75/23 N=175 n (%)	PHEN/TPM 7.5/46 N=366 n (%)	PHEN/TP M 15/92 N=1092 n (%)
Subjects with TEAE	239 (84.2)	51 (78.5)	114 (86.4)	440 (90.2)	947 (74.2)	141 (80.6)	310 (84.7)	937 (85.8)
Treatment-emergent SAE	8 (2.8)	1 (1.5)	8 (6.1)	16 (3.3)	44 (3.4)	5 (2.9)	6 (1.6)	41 (3.8)
TEAE resulting in study drug discontinuation	22 (7.7)	6 (9.2)	13 (9.8)	58 (11.9)	109 (8.5)	22 (12.0)	45 (12.3)	216 (19.8)

Source: Applicant's Table 8 CV risk assessment – CR submission

Within the targeted medical event of cardiac disorders, there were a higher percentage of heart rate outliers with a cardiac disorder event compared to non-heart rate outliers. Within each subgroup, a higher proportion of PHEN/TPM-treated subjects had a cardiac disorder TME compared to placebo-treated subjects. The majority of the events were in the cardiac arrhythmia subclass and consisted mainly of the preferred term palpitations.

Table 64: Targeted Medical Event: Cardiac Disorders Class/subclass/preferred term in heart rate outliers and non-outliers – 1-year cohort (safety set)

	With heart rate elevations				Without heart rate elevations			
TME Class	Placebo	PHEN/TPM	PHEN/TPM	PHEN/TPM	Placebo	PHEN/TPM	PHEN/TPM	PHEN/TPM
TME Subclass		3.75/23	7.5/46	15/92		3.75/23	7.5/46	15/92
Preferred term	N=284 n (%)	N=65 n (%)	N=132 n (%)	N=488 n (%)	N=1277 n (%)	N=175 n (%)	N=366 n (%)	N=1092 n (%)
Cardiac disorders class	3 (1.1)	3 (4.6)	12 (9.1)	28 (5.7)	33 (2.6)	1 (0.6)	12 (3.3)	50 (4.6)
Cardiac arrhythmia (SMQ) subclass								
Cardiac arrhythmia (SMQ) subclass	2 (0.7)	2 (3.1)	10 (7.6)	27 (5.5)	26 (2.0)	1 (0.6)	11 (3.0)	47 (4.3)
Palpitations	1 (0.4)	1 (1.5)	4 (3.0)	7 (1.4)	11 (0.9)	1 (0.6)	8 (2.2)	20 (1.8)
Tachycardia	0	1 (1.5)	1 (0.8)	5 (1.0)	1 (0.1)	0	1 (0.3)	6 (0.5)
Heart rate increased	0	0	0	5 (1.0)	1 (0.1)	0	2 (0.5)	7 (0.6)
Syncope	0	0	2 (1.5)	3 (0.6)	4 (0.3)	0	0	3 (0.3)
Atrial fibrillation	0	0	1 (0.8)	2 (0.4)	2 (0.2)	0	0	1 (0.1)
Syncope vasovagal	0	0	1 (0.8)	2 (0.4)	0	0	1 (0.3)	1 (0.1)
Arrhythmia	0	0	1 (0.8)	1 (0.2)	0	0	0	1 (0.1)
Bundle branch block right	0	0	1 (0.8)	0	2 (0.2)	0	0	1 (0.1)
ECG QT prolonged	0	0	0	1 (0.2)	1 (0.1)	0	0	0
Extrasystoles	0	0	0	1 (0.2)	0	0	0	0
Heart rate irregular	0	0	0	1 (0.2)	0	0	0	1 (0.1)
Sinus bradycardia	0	1 (1.5)	0	0	0	0	0	0
Sinus tachycardia	0	0	0	1 (0.2)	0	0	0	0
Supraventricular extrasystoles	0	0	1 (0.8)	0	0	0	0	0
Ventricular extrasystoles	0	0	0	1 (0.2)	1 (0.1)	0	0	1 (0.1)
ECG abnormal	0	0	0	0	3 (0.2)	0	0	0
ECG repolarization abnormality	0	0	0	0	0	0	0	2 (0.2)
Loss of consciousness	0	0	0	0	0	0	1 (0.3)	1 (0.1)
AV block first degree	1 (0.4)	0	0	0	0	0	0	1 (0.1)
Bradycardia	0	0	0	0	0	0	0	1 (0.1)
Cardiac flutter	0	0	0	0	0	0	0	1 (0.1)

	With heart rate elevations				Without heart rate elevations			
TME Class	Placebo	PHEN/TPM	PHEN/TPM	PHEN/TPM	Placebo	PHEN/TPM	PHEN/TPM	PHEN/TPM
TME Subclass		3.75/23	7.5/46	15/92		3.75/23	7.5/46	15/92
Preferred term	N=284 n (%)	N=65 n (%)	N=132 n (%)	N=488 n (%)	N=1277 n (%)	N=175 n (%)	N=366 n (%)	N=1092 n (%)
Cardio-respiratory arrest	0	0	0	0	1 (0.1)	0	0	0
Ischemic heart disease (SMQ) subclass								
Ischemic heart disease (SMQ) subclass	1 (0.4)	1 (1.5)	2 (1.5)	1 (0.2)	7 (0.5)	0	1 (0.3)	3 (0.3)
Myocardial infarction	0	1 (1.5)	1 (0.8)	1 (0.2)	0	0	0	1 (0.1)
Blood creatine phosphokinase increase	1 (0.4)	0	1 (0.8)	0	0	0	0	0
Coronary artery disease	0	0	0	1 (0.2)	5 (0.4)	0	0	0
Angina pectoris	0	0	0	0	2 (0.2)	0	0	2 (0.2)
Acute coronary syndrome	0	0	0	0	0	0	0	1 (0.1)
Arteriosclerosis coronary artery	0	0	0	0	0	0	1 (0.3)	0
Myocardial ischemia	0	0	0	0	1 (0.1)	0	0	0
Source: Applicant's Supporting Table 30-31 CV risk assessment report Data from studies OB-202/DM-230, OB-302, and OB-303								

In the 1-year safety cohort, there were six subjects with atrial fibrillation [placebo 2/1561 (0.1% and PHEN/TPM 4/2318 (0.2%)]. Because elevations in heart rate are associated with atrial fibrillation, it should be noted there were 3 heart rate outliers treated with PHEN/TPM who reported an adverse event of atrial fibrillation versus none treated with placebo. In the non-heart rate outlier group, there were 2 subjects treated with placebo and 1 subject treated with high-dose PHEN/TPM with an adverse event of atrial fibrillation. Of the six subjects in the 1-year safety cohort who reported atrial fibrillation, three (1 placebo, 2 PHEN/TPM-treated) were considered SAEs due to hospitalization due to a cardiac arrhythmia and were included in the sponsor's major adverse cardiovascular event analyses.

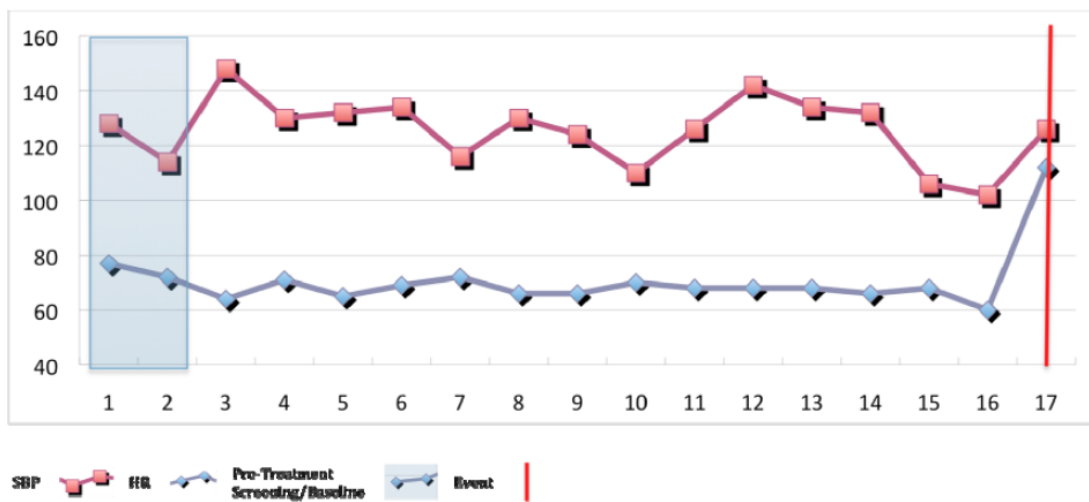
The narratives of these events follow with a temporal plot of SBP and HR. The horizontal axis corresponds to Visits. Visit 1 corresponds to the screening visit and Visit 2 represents baseline. Subject 160-109, treated with mid-dose PHEN/TPM, had an increase in heart rate of 20 bpm over baseline at a clinic visit approximately two-weeks prior to the event. Subject 153-036, treated with high-dose PHEN/TPM, experienced an elevation in heart rate once treatment started which was sustained until Visit 10. His heart rate decreased over the next several clinic visits to his baseline value and was slightly below his baseline heart rate when he was found to be in atrial fibrillation.

Placebo

Subject 160-100: atrial fibrillation with rapid ventricular response Baseline BP 114/66 HR 72

A 67-year-old Caucasian female with a history of obesity, signed informed consent on 12-Mar-2008 and was randomized to placebo on (b) (6). The last dose of study drug was on Study Day 393 (b) (6). The subject completed the study per protocol on Study Day 394 (b) (6). On that same date, during the final study visit, the subject underwent a routine study electrocardiogram, which revealed atrial fibrillation with rapid ventricular response and a heart rate of 110 bpm. The subject was transferred to the emergency room for evaluation and was subsequently admitted to the hospital. Physical examination on admission revealed a blood pressure of 180/96 mmHg, respirations of 24 breaths per minute, and an irregular heart rate of 140 bpm. The subject denied shortness of breath, palpitations, nausea, diaphoresis, orthopnea, paroxysmal nocturnal dyspnea, or dyspnea on exertion. Laboratory testing revealed a creatine phosphokinase of 86 U/L, creatine kinase-MB of 0.6 ng/mL, and troponin I <0.10 ng/mL. A chest X-ray was normal. An electrocardiogram revealed atrial fibrillation with rapid ventricular response, inferior and lateral ST-T changes possibly due to myocardial ischemia or rhythm. An echocardiogram revealed borderline concentric left ventricular hypertrophy with an ejection fraction of 50–55%. Treatment of the event included enoxaparin, aspirin, warfarin, metoprolol, and diltiazem. The subject recovered from the event and was discharged from the hospital on (b) (6). The subject's medical history includes hypertension, dyslipidemia, tonsillectomy, tubal ligation, arthritic joint discomfort, urinary tract infection, postmenopausal status, heart murmur, and recurrent yeast infections. Concomitant medications included ibuprofen, multivitamin, vitamin D, lisinopril, and lovastatin. The investigator considered the event of atrial fibrillation with rapid ventricular response as mild in severity and not related to study drug.

160-100 Systolic Blood Pressure and Heart Rate:

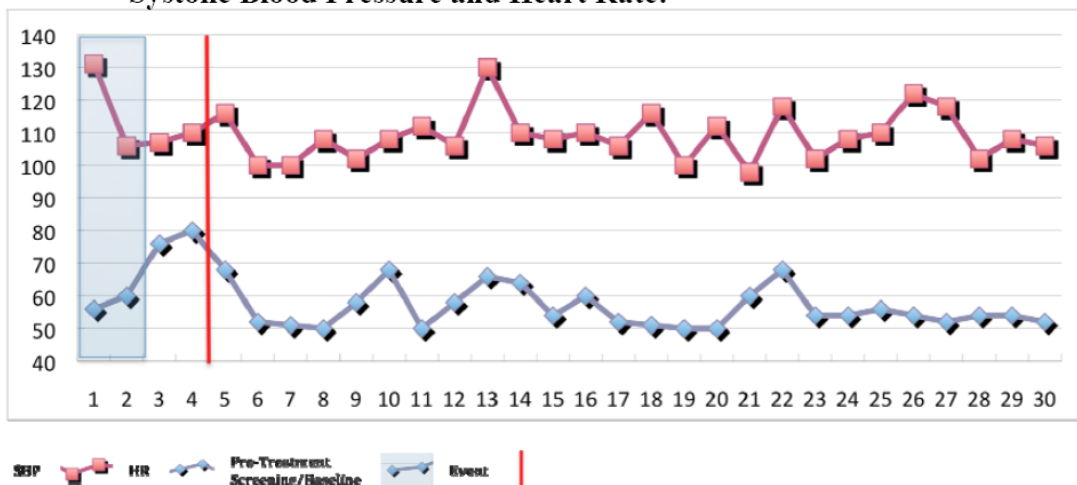


PHEN/TPM mid-dose

Subject 160-109: atrial fibrillation. Baseline BP 106/74 HR 60

A 67-year-old Caucasian female with a history of obesity, signed informed consent on 13-Mar-2008 and was randomized to PHEN/TPM 7.5/46 mg on (b) (6). At Visit 3, April 10, 2008, BP was 107/76 and HR was 76. At Visit 4, April 24, 2008, BP was 110/72 and HR was 80 (a 20 bpm increase from baseline). On Study Day 43 (b) (6), 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 (b) (6). The subject was discharged from the hospital on Study Day 44 (b) (6). The study drug was interrupted from Study Day 43 (b) (6) to Study Day 48 (b) (6). The subject was placed on atenolol from May 9 to May 13 and from June 13 to June 24. She was placed on metoprolol on July 3 12.5 mg for prophylaxis for arrhythmia and was continuing medication at the end of the study. 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. The investigator considered the event of atrial fibrillation as severe in severity and not related to study drug.

160-109 Systolic Blood Pressure and Heart Rate:

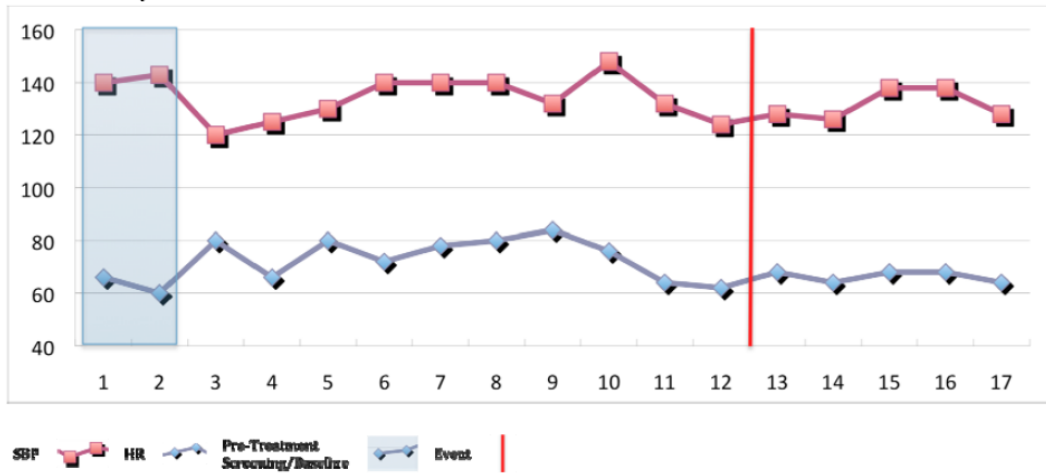


PHEN/TPM high-dose

Subject 153-036: atrial fibrillation Baseline BP 143/95, HR 60

A 59-year-old Caucasian male with a history of obesity, signed informed consent on 23-Jan-2008 and was randomized to PHEN/TPM 15/92 mg on (b) (6). On February 20, 2008, BP was 120/80 and HR was 80 bpm. On April 2, 2008, BP 130/90 and HR 80 bpm, On July 23, 2008, BP was 132/84 and HR was 84 bpm. On August 20, 2008 BP 148/100 and HR 76 bpm. On September 24, 2008 BP 132/84, HR 64 bpm. On October 15, 2008, BP 124/78, HR 62 bpm. On Study Day 274 (b) (6), 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. On an unknown date during the hospitalization, the atrial fibrillation spontaneously converted to normal sinus rhythm. On Study Day 277 (b) (6), the subject recovered from the event and was discharged from the hospital. The study drug was interrupted from Study Day 245 (b) (6) to Study Day 278 (b) (6). 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. The investigator considered the event of atrial fibrillation as moderate in severity and not related to study drug.

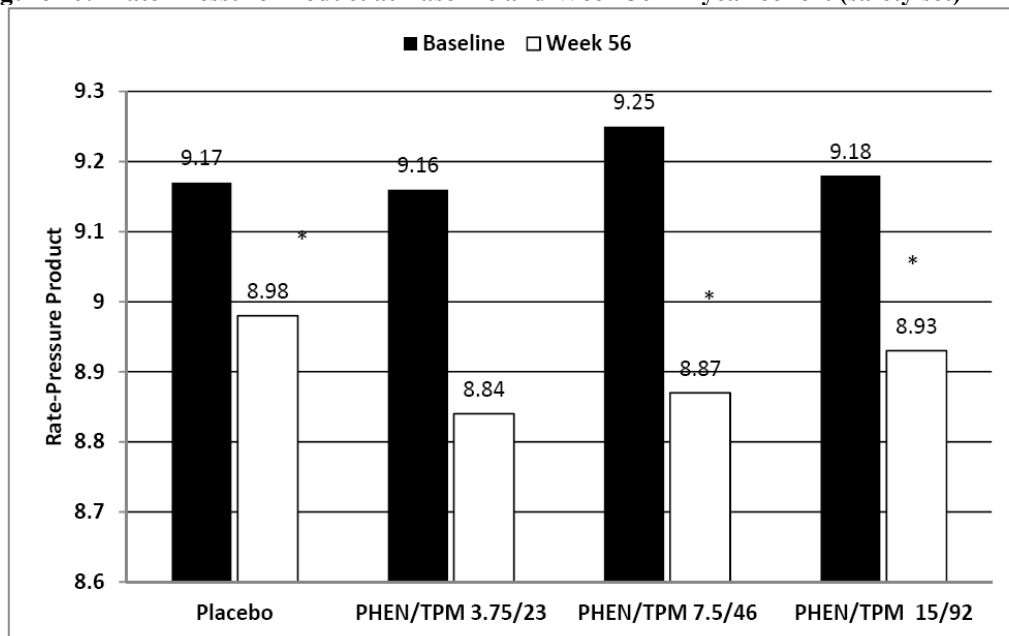
153-036 Systolic Blood Pressure and Heart Rate:



Rate-pressure product

The rate-pressure product (RPP) is defined as the product of heart rate (bpm) and SBP. The applicant divided the RPP by 1000 for this analysis. RPP has been shown to correlate with myocardial oxygen demand. The applicant analyzed the change in RPP from baseline to Week 56 with LOCF for the 1-year safety cohort and several subgroups. There were no statistically significant differences between the PHEN/TPM-treated groups compared to placebo-treated groups (Figure 10).

Figure 10: Rate-Pressure Product at Baseline and Week 56 – 1-year cohort (safety set)



* = significant change from baseline within treatment group.

Note: comparison of PHEN/TPM groups to placebo were not significant.

Source: Applicant's Figure 3, CV risk assessment report, CR submission

The RPP was also calculated for the subgroups with/without heart rate elevations and with/without hypertension (Table 65).

For heart rate outliers, statistically significant increases from baseline in RPP were observed in all treatment groups, although numerically smaller in PHEN/TPM-treated versus placebo-treated.

For subjects with hypertension at baseline, statistically significant mean reductions in RPP were observed in the placebo, mid- and high-dose PHEN/TPM groups. None of the comparisons between placebo and PHEN/TPM groups were statistically significant.

Table 65: Change in RPP at Week 56 with LOCF – 1-year cohort, heart rate subgroups, hypertension subgroups

Treatment	N [1]	Baseline [2] Mean (SD)	Week 56 With LOCF [3] Mean (SD)	Change [4]			
				Mean (SD)	LS Mean (SE)	P-value	
						Within	vs Placebo
1-Year Cohort							
Placebo	1531	9.16 (1.55)	9.01 (1.61)	-0.15 (1.67)	-0.13 (0.05)	0.0173	
PHEN/TPM 3.75/23	234	8.86 (1.46)	8.77 (1.47)	-0.09 (1.54)	-0.19 (0.11)	0.0751	0.5470
PHEN/TPM 7.5/46	488	9.27 (1.59)	8.97 (1.63)	-0.30 (1.73)	-0.23 (0.08)	0.0044	0.1686
PHEN/TPM 15/92	1551	9.14 (1.58)	8.95 (1.52)	-0.19 (1.69)	-0.18 (0.05)	0.0007	0.3306
Subjects With Heart Rate Elevations							
Placebo	284	8.77 (1.70)	9.57 (1.84)	0.80 (1.70)	0.83 (0.11)	<0.0001	
PHEN/TPM 3.75/23	65	8.36 (1.46)	9.14 (1.71)	0.78 (1.57)	0.69 (0.21)	0.0010	0.5376
PHEN/TPM 7.5/46	132	8.99 (1.77)	9.42 (1.68)	0.44 (1.94)	0.54 (0.16)	0.0006	0.0798
PHEN/TPM 15/92	488	8.77 (1.73)	9.29 (1.68)	0.52 (1.69)	0.55 (0.09)	<0.0001	0.0118
Subjects Without Heart Rate Elevations							
Placebo	1247	9.25 (1.50)	8.88 (1.52)	-0.37 (1.59)	-0.42 (0.06)	<0.0001	
PHEN/TPM 3.75/23	169	9.06 (1.41)	8.63 (1.35)	-0.43 (1.39)	-0.55 (0.12)	<0.0001	0.2580
PHEN/TPM 7.5/46	356	9.38 (1.50)	8.80 (1.58)	-0.58 (1.56)	-0.58 (0.09)	<0.0001	0.0561
PHEN/TPM 15/92	1063	9.30 (1.48)	8.79 (1.42)	-0.51 (1.59)	-0.53 (0.06)	<0.0001	0.0478
Subjects With Hypertension at Baseline							
Placebo	616	9.66 (1.65)	9.28 (1.69)	-0.39 (1.79)	-0.34 (0.08)	<0.0001	
PHEN/TPM 3.75/23	33	9.76 (1.99)	9.22 (1.53)	-0.54 (1.76)	-0.39 (0.28)	0.1701	0.8597
PHEN/TPM 7.5/46	256	9.56 (1.64)	9.19 (1.68)	-0.37 (1.78)	-0.38 (0.12)	0.0017	0.6816
PHEN/TPM 15/92	633	9.56 (1.74)	9.09 (1.62)	-0.47 (1.85)	-0.49 (0.08)	<0.0001	0.0796
Subjects Without Hypertension at Baseline							
Placebo	915	8.83 (1.37)	8.83 (1.52)	0.00 (1.57)	0.02 (0.08)	0.8089	
PHEN/TPM 3.75/23	201	8.72 (1.30)	8.70 (1.45)	-0.02 (1.49)	-0.02 (0.12)	0.8644	0.7202
PHEN/TPM 7.5/46	232	8.96 (1.47)	8.73 (1.54)	-0.23 (1.66)	-0.18 (0.12)	0.1330	0.0633
PHEN/TPM 15/92	918	8.84 (1.39)	8.85 (1.44)	0.01 (1.53)	0.04 (0.08)	0.6481	0.7950
1. N is the number of subjects with values at both time points.							
2. Baseline is the last measurement obtained on or before the first dose date of double-blind study drug.							
3. Week 56 with LOCF is the last available measurement during the double-blind treatment period.							
4. Least-squares mean, SE, and two-sided p-value are from an analysis of covariance model with treatment and study as fixed effects and baseline as a covariate.							
LOCF = last observation carried forward; LS = least squares; PHEN/TPM = VI-0521 fixed-dose combination;							
SD = standard deviation; SE = standard error.							
Sources: Supporting Post-text Tables 32, 33, 34, 35, and 36							

Source: Applicant's Table 9, CV risk assessment report – CR submission

The change in rate-pressure product for the 2-year cohort at Week 56 and Week 108/Early Termination visit is presented in the table below. The changes in RPP in the PHEN/TPM-treated group were directionally favorable and similar to placebo.

Table 66: Change in RPP for the two-year cohort at Week 56 and Week 108/Early termination – 2-year cohort (safety set)

	Placebo N=227	PHEN/TPM 7.5/46 N=153	PHEN/TPM 15/92 N=295
n [1]	227	153	295
Baseline [2] mean (SD)	9.06 (1.61)	9.21 (1.49)	9.29 (1.61)
Week 56 mean (SD)	8.72 (1.50)	8.92 (1.63)	8.90 (1.48)
Mean change (SD)	-0.34 (1.64)	-0.28 (1.78)	-0.38 (1.68)
n [1]	227	153	295
Week 108/ET mean (SD)	8.8.0 (1.56)	9.01 (15.7)	9.1. (1.55)
Mean change	-0.26 (1.69)	-0.20 (1.84)	-0.13 (1.64)
Rate-pressure Product (RPP) is calculated as (heart rate * systolic blood pressure) * 10 ⁻³ . [1] n is the number of subjects with both baseline and post-baseline measurements [2] Baseline is defined as the last measurement obtained on or before the first dose date of double-blind study medication of OB-303.			

It is uncertain whether these changes in RPP have any predictive value regarding risk of major adverse cardiovascular events. However, it is reassuring that the PHEN/TPM-treated groups did not show large directionally unfavorable mean differences from placebo-treated groups.

Predictive indices for Major Cardiovascular Events

The applicant employed two indices, the Cooper Clinic Mortality Risk Index⁴ and Framingham Risk Score (FRS), to assess whether treatment with PHEN/TPM changed risk scores.

The Cooper Clinic Mortality Risk Index (published in 2005) was derived and validated in men age 20-69 years old without a history of coronary heart disease, stroke, or cancer at baseline. The participants were predominantly non-Hispanic whites and college graduates. The algorithm factored in blood pressure, lipids, age, heart rate, smoking status, cardiorespiratory fitness, and presence of obesity and diabetes. The purpose of the index was to predict 15-year all-cause mortality risk. The largest and only statistically significant LS mean (SE) placebo-subtracted difference in the Cooper Risk Mortality Index score was between the high-dose PHEN/TPM group and placebo group (LS mean (SE) -1.08 (0.42), p=0.01) in the pooled studies OB-302 and OB-303 at Week 56.

The change in Framingham 10-year risk of coronary heart disease was evaluated in one of the pivotal Phase 3 trials, OB-303. At baseline the mean FRS was <5% overall, which is considered low risk. The LS mean difference from the placebo group was small, -0.5% and -0.7%, in the

⁴ Janssen I et al. The Cooper Clinic Mortality Risk Index: Clinical score sheet for men. Am J Prev Med 2005;23 (3):2005

mid- and high-dose PHEN/TPM groups, respectively but achieved statistical significance (0.0052 and <0.0001, mid- and high-PHEN/TPM groups, respectively).

Although the trend is reassuring, the clinical implication of these small mean changes in the Cooper Clinic Mortality Risk Index and Framingham Risk Scores with PHEN/TPM over placebo, especially for women, is unclear. Longer-term follow-up is needed to examine if this change in risk score translates into improvement in cardiovascular co-morbidity and mortality in obese adults.

Major Cardiovascular Event Analysis

The PHEN/TPM clinical development program was not designed to seek a cardiovascular prevention indication or rule out cardiovascular risk; therefore, the clinical trials were not sufficiently powered to evaluate the effect of PHEN/TPM treatment on cardiovascular outcomes. As a result, recruitment of an appropriate at-risk population, prespecification of cardiovascular events of interest, and *a priori* adjudication of major adverse cardiovascular events was not incorporated into the clinical trial protocols. As part of the response to the CR letter, the applicant conducted post-hoc analyses of MACE in the PHEN/TPM clinical program.

Definitions for each of these endpoints are as follows:

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

The sponsor calculated annualized incidence rates, hazard ratios by Cox proportional hazard analysis, and 95% confidence intervals which are presented in Table 67. Figure 11 is a forest plot of the hazard ratio and 95% confidence interval for the comparison of total PHEN/TPM versus placebo for the incidence of cardiovascular events in each of the composite cardiovascular endpoints.

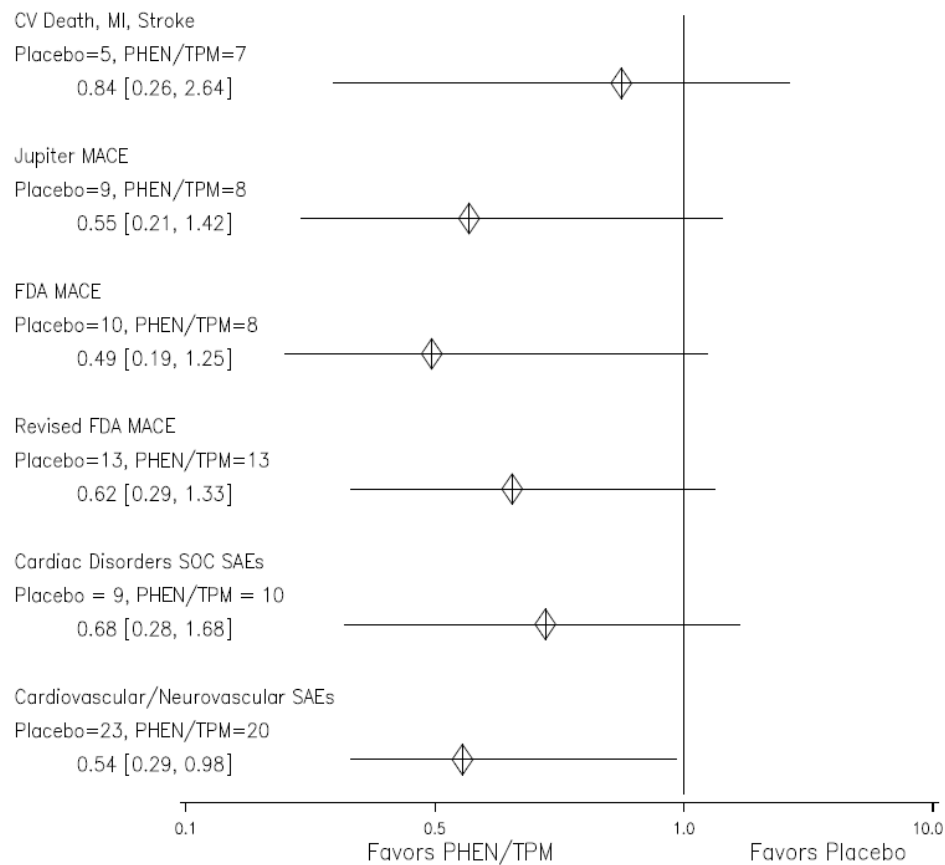
For each composite endpoint, the number of events was small. This is consistent with expectations, given that the population recruited for the PHEN/TPM clinical development program was mostly younger women. A by-subject listing of the terms captured by these cardiovascular endpoint definitions is listed in Appendix B.

Table 67: Annualized incidence rates for cardiovascular event outcomes – all exposed subjects

Event Category	Annualized Incidence Rate					HR ¹	95% CI
	Placebo (N=1742)	PHEN/TPM 3.75/23 (N=240)	PHEN/TPM 7.5/46 (N=604)	PHEN/TPM 15/92 (N=1737)	PHEN/TPM Total (N=2581)		
CV death, MI, Stroke	0.3	0.5	0.3	0.2	0.3	0.84	0.26, 2.64
Jupiter MACE	0.6	0.5	0.3	0.3	0.3	0.55	0.21, 1.42
FDA MACE	0.6	0.5	0.3	0.3	0.3	0.49	0.19, 1.25
Revised FDA MACE	0.8	0.5	0.6	0.5	0.5	0.62	0.29, 1.33
Cardiac SOC SAEs	0.6	0.5	0.6	0.3	0.4	0.68	0.28, 1.68
Cardiovascular/ Neurovascular SAEs	1.5	1.0	0.9	0.7	0.8	0.54	0.29, 0.98

1. Hazard ratio is from a univariate Cox proportional hazards regression analysis comparing PHEN/TPM total to Placebo. CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SAE = serious adverse event; SOC = system organ class.
Source: [Supporting Post-text Table 39](#)

Figure 11: Forest plot for comparison of PHEN/TPM to placebo for incidence of major adverse cardiovascular events – All exposed subjects



CV = cardiovascular; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; MACE = major adverse cardiovascular events; MI = myocardial infarction; PHEN/TPM = VI-0521 fixed-dose combination of phentermine and topiramate; SAE = serious adverse event; SOC = system organ class.
Source: [ISS Post-text Table S39.1](#)

Highlights from the PHEN/TPM cardiovascular risk assessment

- In the 1-year safety cohort, the mean reduction in SBP over placebo was 3.1 mmHg in mid- and high-dose PHEN/TPM subjects ($p < 0.0001$ for both doses versus placebo).
- In the 1-year safety cohort, the mean reduction in DBP over placebo was 1.4 mmHg ($p = 0.0044$ versus placebo) and 1.0 mmHg ($p = 0.0023$ versus placebo) in mid- and high-dose PHEN/TPM subjects, respectively.
- In the 1- and 2-year safety cohorts, higher proportions of subjects treated with placebo compared to those treated with PHEN/TPM had categorical increases in blood pressure.
- In the 1-year safety cohort, mean heart rate increased by 0.6 bpm in the mid-dose PHEN/TPM group compared to placebo ($p = 0.29$) and by 1.6 bpm in the high-dose PHEN/TPM group compared to placebo ($p < 0.0001$).
- In the 1-year and 2-year safety cohorts, higher proportions of subjects treated with PHEN/TPM compared to subjects treated with placebo had categorical increases in heart rate.
- In the 2-year safety cohort, the mean treatment difference in SBP over placebo was -0.8 mmHg ($p = 0.63$ versus placebo) in mid-dose PHEN/TPM-treated subjects and +0.3 mmHg ($p = 0.78$ versus placebo) in high-dose PHEN/TPM-treated subjects.
- In the 2-year safety cohort, the mean treatment difference in DBP over placebo was +0.1 mmHg ($p = 0.95$ versus placebo) in mid-dose PHEN/TPM-treated subjects and +0.7 mmHg ($p = 0.49$ versus placebo) in high-dose PHEN/TPM-treated subjects.
- In the 2-year safety cohort, mean heart rate increased by 0.9 bpm in the mid-dose PHEN/TPM group compared to placebo ($p = 0.47$) and by 1.3 bpm in the high-dose PHEN/TPM group compared to placebo ($p = 0.18$).
- Subgroups based on baseline characteristics such as age, sex, race, hypertension, diabetes in the 1-year cohort, demonstrated similar changes in blood pressure and heart rate that were consistent with the total 1-year summary results.
- Consistent with “regression to the mean,” subjects with baseline heart rate < 60 bpm experienced the greatest mean increases in heart rate and subjects with baseline heart rate > 90 bpm experienced mean decreases in heart rate across all treatment groups. In subjects with baseline heart rate between 60 and 90 bpm increases in mean heart rate were consistent with the overall pattern of heart rate in the 1-year cohort with a 0.8 bpm increase over placebo in the mid-dose PHEN/TPM group and 1.6 bpm increase over placebo in the high-dose PHEN/TPM group.
- Overnight polysomnogram measurements of heart rate showed a reduction in heart rate in both placebo and PHEN/TPM groups from baseline. However, daytime heart rate measurements demonstrated a mean increase of 6 bpm over placebo with high-dose PHEN/TPM-treatment at Week 28.
- An analysis of the rate-pressure product demonstrated similar mean reductions in all treatment groups in the 1-year cohort.
- In heart rate outliers, the rate-pressure product increased in all treatment groups, however, the RPP in PHEN/TPM-treated groups was equal or lower than the placebo-treated group.
- Two predictive indices of cardiovascular risk, the Cooper Clinic Mortality Risk Score and Framingham Risk Score, showed small reductions in scores with high-dose PHEN/TPM treatment compared to placebo treatment of -1.1 ($p = 0.01$) and -0.7

($p < 0.0001$), respectively. The clinical implication of these statistically significant small mean changes with PHEN/TPM over placebo, especially for women, is unclear.

- The traditional MACE composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke occurred in 12 subjects (5 placebo, 7 PHEN/TPM) with a hazard ratio of 0.84 (95% CI 0.26, 2.64).

Conclusions regarding PHEN/TPM cardiovascular risk assessment

In a cohort of overweight and obese adults with mostly low-to-moderate baseline cardiovascular risk treated with PHEN/TPM, the observed changes in blood pressure, rate-pressure product, and post-hoc analyses of MACE events were directionally favorable and similar to placebo. Mean heart rate increased with PHEN/TPM treatment versus placebo, and while the differences are small, they were consistent across subgroups and were observed at the end of the 2-year treatment period. It is unknown what the clinical significance of PHEN/TPM's cardiovascular effects and metabolic effects will be in a higher-risk cardiovascular population with chronic treatment. Ultimately, only a long-term, cardiovascular outcome trial can define the effect of PHEN/TPM treatment on risk for major adverse cardiovascular events in an obese at-risk population.

VI. Teratogenic potential of PHEN/TPM

PHEN/TPM development program and pregnancy exposure

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, subjects 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 subjects. There were 34 pregnancies in the PHEN/TPM clinical development program. Of the 19 pregnancies carried to term, newborn examinations did not reveal any major malformations.

Table 68: Number of pregnancies by study and dose

Study	Total	Placebo	Active Comparator	PHEN/TPM 3.75/23	PHEN/TPM 7.5/46	PHEN/TPM 15/92	PHEN/TPM 22.5/138 mg	PHEN/TPM Total
OB-118	1	0	–				1	1
OB-205	2	0	–		2			2
OB-301	8	1	5*	–	2	–		2
OB-302	18	3	–	1	–	14		15
OB-303	3	0	–	–	1	2		3
OB-305	2	1	–	–		1		1
Program	34	5	5	1	5	17	1	24

* TPM46 (1), PHEN15 (2), and TPM92 (2)

PHEN=phentermine; TPM=topiramate; PHEN/TPM=VI-0521 fixed-dose combination of phentermine and topiramate

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 PHEN/TPM if approved for weight loss.

Experience with topiramate and pregnancy exposure

During the initial NDA review, concern was raised regarding the teratogenic potential of topiramate based on data from the North American Antiepileptic Drug Pregnancy Registry (NAAPR) in 2010. At that time, topiramate monotherapy-exposed pregnancies had a higher prevalence of MCM (3.8%, 11/289) versus an unexposed control group (1.3%, 5/372) for a relative risk of 2.8 (95% CI 1.0-8.1). Four infants exposed to topiramate had cleft lip, 2 (0.69%) of them were isolated which was approximately 10-fold higher than the background prevalence cited for isolated cleft lip as 0.07%.⁵

At the EMDAC meeting in 2010, the applicant presented a meta-analysis of data from four pregnancy registries of topiramate-monotherapy exposure. The applicant calculated the congenital malformation rate across these registries and compared this rate to the malformation rate in pregnancies of women with untreated epilepsy. The results of the applicant's analysis demonstrated a relative risk of congenital malformations with topiramate exposure of 1.1 (95% CI 0.58 to 2.06) comparing these two groups of pregnant women.⁶

The variable level of malformation risk with different analyses and the potential for large numbers of exposed pregnancies was seen as a significant concern by members of the EMDAC and was cited in the CR letter.

In response to the CR letter, the applicant submitted updated information from several pregnancy registries as well as an updated meta-analysis of all published pregnancy registries for topiramate exposure in utero, the results of a large, population-based cohort study from Denmark, data from two case-control surveillance programs in North America (Slone/CDC study), as well as two applicant-funded retrospective cohort studies from healthcare databases.

Pregnancy Registries

Human pregnancy outcomes with topiramate exposure have been tracked in several pregnancy registries including the North American AED Pregnancy Registry, the UK Pregnancy and Epilepsy Register, the Israeli Pregnancy Registry, and Australian Pregnancy Register.

North American Antiepileptic Drug (AED) Pregnancy Registry

The North American Antiepileptic Drug (AED) Pregnancy Registry (NAAPR) was established at the Massachusetts General Hospital in Boston in December 1996. Enrollment in NAAPR is voluntary and initiated when the woman calls a toll-free number to register. In the initial interview, information regarding medication, condition for which the AED is prescribed, other exposures such as alcohol and smoking history, and demographics are obtained. The second interview occurs at 7 months gestation, and the third interview 8 to 12 weeks after the expected date of delivery. With written consent, medical records are obtained regarding the infant and mother's health status.

⁵ Hernandez-Diaz S et al. Comparative safety of topiramate during pregnancy. Birth Defects Res A Clin Mol Teratol. 2010 May;88 (5):408.

⁶<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugs/AdvisoryCommittee/ucm227049.htm> Accessed January 2, 2012

The definition used for a major congenital malformation (MCM) in this registry is a structural abnormality with surgical, medical or cosmetic importance. The findings are reviewed by a teratologist, blinded to exposure status, to determine whether the abnormality is included or excluded. Features excluded as not being a major malformation are:⁷

- minor anomalies (transverse palmar crease);
- birth marks (hemangiomas);
- positional deformations (hip dislocation in a breech presentation);
- a complication of prematurity, defined as birth before 37 weeks gestation (undescended testes, patent ductus arteriosus);
- chromosome abnormalities (Down Syndrome);
- genetic disorder (achondroplasia, Holt-Oram Syndrome);
- a finding in prenatal ultrasound that is not found by examining pediatrician (unilateral renal agenesis);
- biochemical abnormality (hemoglobin abnormality or cystic fibrosis) identified in newborn screening;
- finding by echocardiogram with no physiologic significance (tiny atrial septal defect; less than 0.4 cm diameter).
- any functional deficit, such as failing the newborn screening test for hearing

Two comparison populations are used in this pregnancy registry

- External comparison group: Newborn infants at Brigham and Women's Hospital
 - Active Malformations Surveillance Program began 1972
 - Malformations noted between birth and 5 days of age
 - Stillborn infants and elective terminations for fetal anomalies are included
 - After excluding chromosome abnormalities and genetic disorders MCM rate of 1.62%
 - Prevalence rates of specific malformations were obtained from 206,224 infants and elective terminations surveyed in the years 1972-74, 1979-2000⁸
- Internal comparison group: Friends and family members of the enrolled women
 - Recruitment began 2003
 - MCM rate 1.3%⁹

The most recent published reports from the NAAPR were presented at the 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management in August 2011.¹⁰ The rate of MCM in topiramate monotherapy-exposed pregnancies in the North American registry was 3.4% (11/321) and of the 11 malformations, there were four infants with OC.

⁷ Holmes LB, Westgate MN. Inclusion and Exclusion criteria for malformations in newborn infants exposed to potential teratogens. Birth Defects Research (Part A) 2011;91:807-12.

⁸ Holmes et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008;70:2152.

⁹ Hernandez-Diaz S et al. Comparative safety of topiramate during pregnancy. Birth Defects Res A Clin Mol Teratol. 2010 May; 88 (5):408

¹⁰ Hernandez-Diaz S et al. Comparative safety of anticonvulsants during pregnancy: seizures or major malformations. Pharmacoepidemiol Drug Saf.2011 Aug;20 (Suppl1):S11.

In March of 2011, a drug safety communication was issued by the FDA and the TOPAMAX label was revised in July 2011 indicating an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy based on the NAAPR data. The relative risk of OC in topiramate-exposed pregnancies in the NAAPR was 9.6 (95% CI 3.6-25.7) as compared to the risk in a background population of untreated women and was reported in the TOPAMAX label.

The applicant has highlighted the difference in rates of MCM in the external (1.6%) and internal (1.3%) control groups used by the NAAPR and those reported by the Center for Disease Control (CDC) of 3% in the general population. It should be noted that the 3% prevalence of birth defects quoted by the CDC reflects data from the Metropolitan Atlanta Congenital Defects Program (MACDP) and is roughly 2.76%.¹¹ The goal of the MACDP is to ascertain the total prevalence of birth defects within the population and collect diagnoses up to 6 years of age. The MACDP includes chromosomal and genetic abnormalities as well as structural.¹² In contrast, because the NAAPR seeks to capture MCM caused by teratogenic drug exposures only it excludes chromosomal and genetic abnormalities.

Australian Pregnancy Register

The Australian Pregnancy Register (APR) was established in 1999 as an observational database. Enrollment in the APR is voluntary. There are 4 telephone interviews, conducted on enrollment, at 7 months of pregnancy, at delivery and after 12 months from delivery. There are three groups of women enrolled, women with epilepsy treated with AEDs, women treated with AED for a non-epilepsy condition, and women with epilepsy with no AED treatment at least in the first half of pregnancy. In January 2012, the APR published data on 31 pregnancies with exposure to topiramate monotherapy.¹³ One MCM of hypospadias was noted. The median daily dose of topiramate was 150 mg. The overall malformation rate for topiramate exposure was 3.2%.

UK Pregnancy and Epilepsy Register

The UK registry enrolls pregnancies from the United Kingdom and Ireland. This registry enrolls a high proportion of eligible pregnancies within its region of interest (estimated 25-33%). To achieve this high enrollment, reporting is done on enrollment and with only one additional follow-up 3 months after birth. Approximately 50% of the pregnancies are enrolled through direct self-referral and the rest through healthcare personnel, as opposed to the NAAPR where every enrollment is self-directed. The UK registry only includes pregnant women with epilepsy with or without ongoing AED treatment. In contrast, the NAAPR includes all women on AEDs at any time during pregnancy irrespective of diagnosis.

¹¹ MMWR weekly January 11, 2008 57;1-5 <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm#fig>. Accessed January 2, 2012

¹² MACDP 40th Anniversary Edition Surveillance Report. Birth Defects Research Part A 2007;79:65-93.

¹³ Vajda FJE et al. J of Clin Neurosci. 2012;19:57-59.

In 2010, The UK register reported a major congenital malformation rate of 3.6% from 83 pregnancies exposed to topiramate monotherapy of 200 mg and higher. Of the three reported malformations, two involved orofacial clefts.¹⁴

Israeli Teratogen Information Service

The outcome of pregnancies of women who contacted the Israeli Teratogen Information Service between January 1996 and December 2006 regarding a pregnancy exposure to topiramate were reported in 2008.¹⁵ There were 29 monotherapy exposed pregnancies and 1 case of pulmonary artery stenosis where the mother received 475 mg of topiramate daily. No further information from this registry has been reported.

In summary the following table lists the current published data regarding topiramate monotherapy and MCM from pregnancy registry data.

Table 69: Pregnancy registry data regarding topiramate exposure and MCM

Source	Malformations	Frequency	Author/Date
North American AED and Pregnancy Registry (NAAPR)	11/321	3.4%	Hernandez-Diaz et al., 2011
UK Epilepsy and Pregnancy Register	3/83	3.6%	Kennedy et al 2010
Israeli Teratogen Information Service	1/29	3.4%	Ornoy et al. 2008
Australian AED Registry	1/31	3.2%	Vajda et al. 2012

As mentioned earlier, the applicant presented at the July 2010 EMDAC meeting, a meta-analysis of pooled data from the four pregnancy registries and compared this malformation rate against the pooled malformation rate in untreated women with epilepsy. The resulting relative risk at that time was 1.1 (95% CI 0.58 to 2.06). As a result, the applicant claimed that topiramate does not pose a significant teratogenic risk when evaluated against this control group of women with untreated epilepsy.

In 2008, the International League Against Epilepsy Commission on Therapeutic Strategies hosted a workshop to discuss pregnancy registries and possible harmonization to determine whether results of registries can be pooled across studies.¹⁶ In their conclusions, representatives from three large independent registries: the UK Epilepsy and Pregnancy Register, the NAAPR and European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) stated the following.

¹⁴ Kennedy F et al. PATH39 malformation risks of antiepileptic drugs in pregnancy: an update from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry. 2010 Nov;81 (11):e18.

¹⁵ Ornoy A et al. The outcome of pregnancy following topiramate treatment: A study on 52 pregnancies. Reprod Tox 2008;25:388-89.

¹⁶ Tomson T et al. Pregnancy registries: Differences, similarities, and possible harmonization. Epilepsia 2010; 51 (5):909-15.

It is clear that the registries are too different in many respects to make general pooling of data meaningful....Instead, they can be regarded as complementary, and the existence of different distinct registries should be seen as major asset allowing observations from one study to be confirmed or refuted by others.

Therefore, due to differences in malformation definitions, ascertainment of diagnoses, recruitment practices, and difference in registry goals, one must interpret with caution, any comparisons between registries and combining of registries to determine the relative risks of MCM.

FDA Adverse Event Reporting System (AERS)

With the original NDA submission, the FDA Adverse Event Reporting System (AERS) was mined for pregnancy adverse outcomes with topiramate and phentermine monotherapy over the period 1997- 2009. This analysis generated 130 reports, 64 of which were considered analyzable for topiramate monotherapy exposure. When information on dosing and timing of exposure was 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.

Following re-submission of the NDA in 2011, the AERS database was mined again for new reports of adverse neonatal events associated with topiramate gestational exposures submitted in 2010 and 2011. A total of 52 spontaneous reports of adverse neonatal events associated with topiramate administration to pregnant women were retrieved from AERS. Out of these, 24 reports (20 duplicates and 4 irrelevant - exposures not prenatal) were excluded from further review. The remaining 28 reports (containing a total of 32 cases) were all cases of congenital malformations. The reporting frequency of OC overwhelmingly dominated over all other types of congenital malformations reported to FDA during 2010-11. OC accounted for over two thirds (20/32; 62.5%) of all malformations reported. This was in agreement with and reinforces our previous observation about the predominant reporting frequency of OC relative to other malformations in association with prenatal topiramate exposure for the period up to 2009.

Of the 20 cases of OC in which topiramate dosage was reported, four were exposed to 100 mg or less, three were exposed to 200 mg and one was exposed to greater 200 mg of topiramate. All exposures occurred in the first trimester of pregnancy.

Danish population study

Please refer to the attached document from the FDA Division of Epidemiology I (DEPI) which reviews the strengths and limitations of this study. Briefly the study is summarized below.

Danish epidemiologists published a population-based cohort study whose primary objective was to study the association between the use of five newer-generation antiepileptic drugs (lamotrigine, oxcarbazepine, topiramate, gabapentin, and levetiracetam) during the first trimester of pregnancy and risk of any MCM of all live births in Denmark from January 1996 through September 2008.

Of the 1532 infants exposed to these 5 AEDs, 49 (3.2%) were diagnosed with a major malformation compared with 19,911 (2.4%) of the 836,263 infants who were not exposed to an AED [adjusted prevalence odds ratio of 0.99 (95% CI 0.72-1.36)]. A major malformation was diagnosed in 5 out of 108 infants exposed topiramate for an adjusted prevalence odds ratio of 1.44 (95% CI 0.58-3.58) (Table 70).

Table 70: Association between first trimester exposure and major malformations

First Trimester Exposure	No. of Women	No. (%) Birth Defects	Crude POR (95% CI)	Adjusted POR (95% CI)
None	836,263	19,911 (2.4)	1.0 (Reference)	1.0 (Reference)
AED*	1532	49 (3.2)	1.35 (1.02–1.80)	0.99 (0.72–1.36)
Topiramate	108	5 (4.6)	1.99 (0.81–4.88)	1.44 (0.58–3.58)
* lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam POR=prevalence odds ratio; CI=confidence interval; AED=antiepileptic drug				

Source: Applicant's Table 7, PHEN/TPM Teratogenic potential review CR submission

One of the infants exposed to topiramate was born with a cleft lip, cleft palate and hypospadias. In an exploratory analysis by the FDA's Division of Epidemiology the estimated unadjusted crude prevalence odds ratio of OC using the Denmark data is provided in the table below. Please note the wide 95% CI which confirms an inadequate sample size.

Table 71: Estimated crude prevalence odds ratio of oral clefts associate with first-trimester topiramate exposure (data source: the Denmark study)

First Trimester Exposure	Number of Women	Number of Oral Cleft	Crude POR (95% CI)
Unexposed to any newer generation AED	836263	1421	Reference
Topiramate	108	1	5.45 (0.77-38.36)

Source: DEPI consult report, December 28, 2011

Ultimately, the Denmark study was not powered to adequately examine the association between topiramate exposure and MCM and OC. Furthermore, in their conclusion from the published paper, the authors stated that "Topiramate does not appear to be a major teratogen, but our study cannot exclude minor to moderate risk for major birth defects."

Wolters Kluwer Study

Please refer to the attached document from the FDA Division of Epidemiology I (DEPI) which reviews the strengths and limitations of this study. Briefly the study is summarized below.

The applicant funded a retrospective cohort study which evaluated data from the Wolters Kluwer Pharma Solutions Source Lx Patient Longitudinal database (January 2003 through December

2010), which tracks patients' pharmacy and medical claims. The study was conducted to evaluate the prevalence of OC and MCM among women exposed to topiramate anytime during pregnancy (n=910 mother/baby pairs) and during the first trimester (n=870 mother/baby pairs) compared to five comparator groups consisting of:

- Women exposed to other AEDs during the first trimester of pregnancy (n=3,615)
- Women with a diagnosis of epilepsy but without topiramate exposure (n=2,607)
- Women with a diagnosis of migraine, no epilepsy, and not treated during pregnancy with acute and preventive migraine drugs (n=26,865)
- Women with a diagnosis of migraine, no epilepsy, treated during pregnancy with acute and preventative migraine drugs (n=2,526)
- Women with a diagnosis of diabetes other than gestational (n=13,063)

For all cohorts, women with exposure to known teratogens or valproic acid were excluded. Mother/baby pairs with chromosomal malformations were also excluded.

Crude (unadjusted) relative risks and 95% CI were calculated to compare the prevalence rates of OC and MCM in the topiramate-exposed cohort with each comparator cohort. The results of OC and MCM prevalence rates in topiramate-exposed pregnancies during the first trimester are listed in the table below.

Table 72: Prevalence rates of OC and MCM in children born to women exposed to topiramate during the first trimester of pregnancy

	n	Oral Clefts		MCMs	
		Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator	Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator
TPM	870	0.23	n/a	4.25	n/a
Other AEDs	3615	0.17	1.39 (0.28–6.85)	3.21	1.33 (0.92–1.90)
Epilepsy	2607	0.31	0.88 (0.18–4.21)	4.33	0.98 (0.68–1.41)
Migraine	26865	0.16	1.47 (0.36–6.06)	3.79	1.12 (0.81–1.55)
Migraine APMD*	2526	0.24	0.95 (0.19–4.68)	4.32	0.99 (0.68–1.42)
Diabetes	13063	0.26	0.88 (0.21–3.67)	6.58	0.65 (0.47–0.89)

* APMD: acute and preventive migraine drugs

Source: Applicant's Table 10, PHEN/TPM teratogenic potential report, CR submission

Limitations of this study are described further in the DEPI consult and include its short time span for data extraction (topiramate approved in 1996 for epilepsy, 2004 for migraine prophylaxis), small sample size, inclusion of topiramate monotherapy and polytherapy with other AEDs in the topiramate-exposed cohort, lack of adjustment for potential confounders such as smoking history and maternal age, misclassification of exposure, and lack of case validation with medical records.

Slone/CDC study

Please refer to the attached document from the FDA Division of Epidemiology I (DEPI) which reviews the strengths and limitations of this study. Briefly the study is summarized below.

Data from two large case-control surveillance programs, Slone Epidemiology Center Birth Defects Study (BDS, 1997-2009) and the Center for Disease Control's National Birth Defects Prevention Study (NBDPS, 1996-2007), were analyzed to evaluate the risk of OC with exposure to topiramate monotherapy during the first trimester of pregnancy.¹⁷

Logistic regression models were used to compare first trimester use of topiramate monotherapy versus no use of antiepileptics between cases and non-malformed controls matched on year and region of birth. The median daily dose of TPM was 100 mg for both cases and controls (range: 25-150 mg). The odds ratio (OR) for MCM was 1.22 (95% CI, 0.19-13.01) in the Slone data and 0.92 (95% CI, 0.26-4.06) in the CDC data; for cleft lip with or without cleft palate, the OR was 10.13 (95% CI, 1.09-129.21) in the Slone data and 3.63 (95% CI, 0.66-20.00) in the CDC data. The pooled OR was 1.01 (95% CI, 0.37-3.22) for MCM and 5.36 (95% CI, 1.49-20.07) for cleft lip with or without cleft palate. There was no case of isolated cleft palate in TPM-exposed pregnancies.

The study concluded that first-trimester use of TPM monotherapy may be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate or overall MCM. This study suggests that while topiramate monotherapy exposure may not be associated with an overall increase in MCM there may be an increased risk of OC.

Table 73: Adjusted OR and 95% confidence intervals for topiramate versus no AED exposure by study

Study	Case/Control	Number of Mothers without any AED Exposure	Number of Mothers with Topiramate Exposure	Adjusted OR (95% CI)
Slone BDS	Control	6,933	2	Reference
	MCMs*	10,503	5	1.22 (0.19-13.01)
	CL/P**	778	3	10.13 (1.09-129.21)
CDC NBDPS	Control	8,434	4	Reference
	MCMs*	23,102	10	0.92 (0.26-4.06)
	CL/P**	2,256	4	3.63 (0.66-20.00)
Combined	Control	15,367	6	Reference
	MCMs*	33,605	15	1.01 (0.37-3.22)
	CL/P**	3,034	7	5.36 (1.49-20.07)

*MCMs: Major congenital malformations

**CL/P: Cleft lip with or without cleft palate

Source: DEPI consult report, December 28, 2011

Limitations of this analysis are further described in the DEPI consult and include possible presence of recall and reporting biases and lack of simultaneous adjustment for study covariates.

Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS)

Please refer to the attached document from the FDA Division of Epidemiology I (DEPI) which reviews the strengths and limitations of this study. Briefly the study is summarized below.

¹⁷ Margulis AV et al. Use of Topiramate in Pregnancy and the Risk of Oral Clefts. Pharmcoepidemiology and Drug Safety 2011;20: S11. Abstract presented at the 27th ICPE 2011 meeting.

The applicant funded a retrospective cohort study which evaluated data from four automated healthcare databases (HealthCore, OptumInsight, Kaiser Northern California, and Thomson Reuters) to estimate the prevalence ratio of MCM and OC in infants exposed to topiramate during the first trimester of pregnancy compared to women without first trimester topiramate exposure. Three cohorts were identified in this analysis.

- Topiramate cohort (TPM): Women exposed to topiramate during the first trimester of pregnancy
- Formerly exposed cohort (FE): Pregnant women formerly exposed to topiramate or any other AED but without exposure to topiramate or other AED during the pregnancy or within 120 days before the estimated conception date.
- Similar medical profile cohort (SMP): Pregnant women matched to the TPM cohort by topiramate indication (epilepsy/seizures, migraine, or other), but without TPM exposure during first trimester of pregnancy or during the 120 days prior to the estimated conception date, in a ratio of 7 SMP cohort members to each TPM cohort member.

A summary of the number of oral cleft cases and the birth prevalence, by center is presented in Table 74. Because of a low birth prevalence of OC in the SMP cohort at HealthCore, the HealthCore database was resampled 1,000 additional times to assess the extent to which the initially reported prevalence was a chance outlier. After an analysis of the 1,000 additional samples, the 0.29 cases of OC per 1,000 births were considered unduly low. Therefore, a comparison of oral cleft prevalence in the topiramate cohort versus the SMP cohort was not performed. Please note that the original sample size calculations estimated 2,300 topiramate exposed mother/baby pairs and 16,000 unexposed mother/baby pairs in order to provide sufficient power to rule out an elevated prevalence ratio for OC of 3.4. The mother/baby sample sizes analyzed was smaller than the protocol-specified sample size.

Table 74: Oral cleft case counts and birth prevalences by research center

Center	Topiramate Cohort		Formerly Exposed Cohort		Similar Medical Profile Cohort	
	Cases ^a (N)	Birth Prevalence ^b (95% CI)	Cases ^a (N)	Birth Prevalence ^b (95% CI)	Cases ^a (N)	Birth Prevalence ^b (95% CI)
HealthCore	3 (495)	6.06 (1.25–17.6)	3 (2,935)	1.02 (0.21–2.98)	1 (3,465)	0.29 (0.01–1.61)
Kaiser	0 (119)	0.00 (0.00–30.5)	4 (2,044)	1.96 (0.53–5.00)	0 (833)	0.00 (0.00–4.42)
OptumInsight	3 (748)	4.01 (0.83–11.7)	8 (4,196)	1.91 (0.82–3.75)	4 (5,235)	0.76 (0.21–1.96)
Thomson Reuters	1 (583)	1.72 (0.04–9.52)	6 (4,337)	1.38 (0.51–3.01)	4 (4,081)	0.98 (0.27–2.51)
Total	7 (1945)	3.60 (0.94–6.26)	21 (13,512)	1.53 (0.84–2.21)	9 (13,614)	0.66 (0.23–1.09)

^a Number of cases (total cohort size).

^b Birth prevalence expressed in cases per 1,000 births.

The preliminary results of the FORTRESS study demonstrated a prevalence ratio for OC standardized by propensity score decile and center of 2.00 (95 % CI 0.71-5.68) for the TPM monotherapy subcohort versus the FE cohort.

(b) (4)

The risks of OCs and MCMs associated with TPM use in the first trimester of pregnancy have not been fully answered in this interim report of the FORTRESS study due to the limited sample size in the TPM monotherapy subcohort, the pending study results using the entire SMP cohort, and the poor data quality issues with the analyses for MCMs.

Highlights from the review of PHEN/TPM teratogenic potential

- The following table lists the latest published data on the frequency of MCM from four pregnancy registries. Experts contend that pregnancy registry data should be viewed as distinct entities which complement each other and recommend against pooling of registries.

Table 75: Summary of published data from pregnancy registries regarding topiramate exposure

Pregnancy registry	Malformations	Frequency	Author/Date
North American AED and Pregnancy Registry (NAAPR)	11/321	3.4%	Hernandez-Diaz et al., 2011
UK Epilepsy and Pregnancy Register	3/83	3.6%	Kennedy et al 2010
Israeli Teratogen Information Service	1/29	3.4%	Ornoy et al. 2008
Australian AED Registry	1/31	3.2%	Vajda et al. 2012

- The following table lists the results of the three studies conducted to evaluate the effect of topiramate exposure on risk of oral clefts and major congenital malformations. All three studies have limitations. The Wolters Kluwer study included women with topiramate monotherapy or polytherapy with other AEDs and therefore the risk attributable to topiramate alone cannot be established. In contrast, FORTRESS and Slone/CDC, used topiramate monotherapy cohorts in their analyses. The Wolters Kluwer study also did not adjust for confounders and therefore the result presented below is an unadjusted estimate of risk. The FORTRESS study excluded a comparison cohort of women when it was determined the resulting oral cleft prevalence in this cohort was unusually low, the sample size of mother/baby pairs to provide sufficient power was not achieved, and the results of FORTRESS have not been validated by medical records. The Slone/CDC data was a combination of two large case-control surveillance programs and adjusted for several potential confounders one by one which ideally would have been performed in a multivariate analysis simultaneously. Furthermore, these databases may have been subject to recall and reporting biases of the participants.

Table 76: Summary of studies evaluating association of topiramate in utero exposure and oral clefts and major congenital malformations

Study	Cohorts compared	Oral clefts		Major congenital malformations	
		Estimated association ¹	95% CI	Estimated association ¹	95% CI
Wolters Kluwer	Topiramate (mono and poly therapy) vs Migraine no meds	1.47	0.36 – 6.06	1.12	0.81 – 1.55
FORTRESS	Topiramate monotherapy vs Formerly exposed to AED	2.00	0.71 – 5.68.	(b) (4)	(b) (4)
Slone/CDC	Topiramate monotherapy vs no AED	5.36	1.49 – 20.07	1.01	0.37 – 3.22
1 Wolters Kluwer: unadjusted relative risk, FORTRESS prevalence ratio, Slone/CDC odds ratio					

Conclusions regarding the teratogenic potential of PHEN/TPM

Since the 2010 EMDAC meeting, there have been three studies (Wolters Kluwer, Slone/CDC, and FORTRESS) conducted to address the risk of major congenital malformations and oral clefts with topiramate exposure in utero. Recognizing the limitations in these studies, the preliminary results of all three were consistent in demonstrating a lack of association between topiramate exposure and risk of major congenital malformations. However, depending on the analysis, topiramate monotherapy exposure in pregnancy is likely to be associated with a two to five-fold increased prevalence of oral clefts.

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
	Anxiety	Somnolence
		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

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Anomalous AV excitation
		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
		Bradyarrhythmia
		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

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Fetal arrhythmia
		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

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Wandering pacemaker
		Withdrawal arrhythmia
		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

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Myocardial ischemia
		Myocardial reperfusion injury
		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

Targeted Medical Event Class	Targeted Medical Event Subclass	Preferred Term
		Drug level increased
		Drug screen
		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

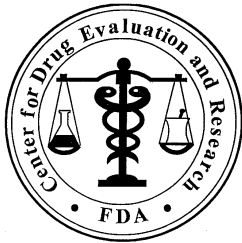
Appendix B: Listing of subjects with cardiovascular events used in CV risk analysis

Subject ID	Study	Treatment	SOC	Preferred Term	Sponsor's Adjudication	CV death, MI, stroke	Jupiter MACE	FDA MACE	Revised FDA MACE	Cardiac disorders SOC SAEs	Cardiovascular or Neurovascular SAE
0203	OB-202	Placebo	General disorders	Chest pain	NA						X
0633	OB-202	Placebo	Nervous system disorders	Cerebrovascular accident	Stroke	X	X	X	X		X
0965	OB-202	Placebo	Cardiac disorders	Cardiac failure congestive	Hospitalization for CHF			X	X	X	X
001-089	OB-204	Placebo	Nervous system disorders	Cerebrovascular accident	Stroke	X	X	X	X		X
102-012	OB-303	PHEN/TPM	Cardiac disorders	Myocardial infarction	Myocardial infarction Coronary revascularization	X	X	X	X	X	X
108-027	OB-303	Placebo	Respiratory disorders	Pulmonary embolism	Hospitalization for other cardiovascular causes				X		X
108-043	OB-303	Placebo	Cardiac disorders	Coronary artery disease	Coronary revascularization		X	X	X	X	X
109-006	OB-303	PHEN/TPM	Respiratory disorders	Pulmonary embolism	Hospitalization for other cardiovascular causes				X		X
109-042	OB-302	PHEN/TPM	Vascular disorders	Deep vein thrombosis	NA						X
115-018	OB-303	Placebo	Cardiac disorders	Myocardial ischemia	NA					X	X
116-036	OB-302	PHEN/TPM	Cardiac disorders	Myocardial infarction	Myocardial infarction Coronary revascularization	X	X	X	X	X	X
120-018	OB-303	PHEN/TPM	Vascular disorders	Hypotension	NA						X
124-040*	OB-303	Placebo	Nervous system disorders	Transient ischemic attack	Transient ischemic attack				X		X
124-040*	OB-303	Placebo	Nervous system disorders	Brain stem infarction	Stroke	X	X	X	X		X

Subject ID	Study	Treatment	SOC	Preferred Term	Sponsor's Adjudication	CV death, MI, stroke	Jupiter MACE	FDA MACE	Revised FDA MACE	Cardiac disorders SOC SAEs	Cardiovascular or Neurovascular SAE
128-047	OB-303	PHEN/TPM	Vascular disorders	Hypertension	NA						X
129-002	OB-303	PHEN/TPM	General disorders	Chest pain	NA						X
130-030	OB-303	Placebo	Cardiac disorders	Coronary artery disease	Coronary revascularization		X	X	X	X	X
131-042*	OB-303	PHEN/TPM	Cardiac disorders	Myocardial infarction	Myocardial infarction Coronary revascularization	X	X	X	X	X	X
131-042*	OB-303	PHEN/TPM	Nervous system disorders	Cerebrovascular accident	Stroke	X	X	X	X		X
131-039	OB-303	PHEN/TPM	Cardiac disorders	Myocardial infarction	Myocardial infarction Coronary revascularization	X	X	X	X	X	X
137-036	OB-303	Placebo	Nervous system disorders	Hemorrhage intracranial	Stroke	X	X	X	X		X
138-146	OB-303	Placebo	Vascular disorders	Hypertension	NA						X
143-037	OB-303	Placebo	Cardiac disorders	Cardio-respiratory arrest	Cardiovascular death	X	X	X	X	X	X
147-038*	OB-302	PHEN/TPM	Respiratory disorders	Pulmonary embolism	Hospitalization for other cardiovascular causes				X		X
147-038*	OB-302	PHEN/TPM	Vascular disorders	Deep vein thrombosis	NA						X
148-160	OB-303	Placebo	General disorders	Non-cardiac chest pain	NA						X
151-014	OB-302	Placebo	General disorders	Chest pain	NA						X
151-072	OB-303	PHEN/TPM	Nervous system disorders	Transient ischemic attack	Transient ischemic attack				X		X
151-079	OB-303	Placebo	Cardiac disorders	Coronary artery disease	Coronary revascularization		X	X	X	X	X

Subject ID	Study	Treatment	SOC	Preferred Term	Sponsor's Adjudication	CV death, MI, stroke	Ju piter MACE	FDA MACE	Revised FDA MACE	Cardiac disorders SOC SAEs	Cardiovascular or Neurovascular SAE
153-036	OB-302	PHEN/TPM	Cardiac disorders	Atrial fibrillation	Hospitalization for cardiac arrhythmia				X	X	X
154-021	OB-303	Placebo	General disorders	Chest pain	NA						X
156-021	OB-303	PHEN/TPM	Nervous system disorders	Cerebral infarction	Stroke	X	X	X	X		X
160-100	OB-303	Placebo	Cardiac disorders	Atrial fibrillation	Hospitalization for cardiac arrhythmia				X	X	X
160-109	OB-303	PHEN/TPM	Cardiac disorders	Atrial fibrillation	Hospitalization for cardiac arrhythmia				X	X	X
165-071	OB-303	PHEN/TPM	Cardiac disorders	Tachycardia	NA					X	X
166-006	OB-303	PHEN/TPM	Vascular disorders	Hypotension	NA						X
172-088	OB-303	PHEN/TPM	Vascular disorders	Deep vein thrombosis	NA						X
172-104	OB-303	Placebo	General disorders	Non-cardiac chest pain	NA						X
172-108	OB-303	Placebo	General disorders	Chest pain	NA						X
177-036	OB-303	Placebo	Vascular disorders	Hypotension	NA						X
178-121*	OB-303	PHEN/TPM	Cardiac disorders	Acute myocardial infarction	Myocardial infarction	X	X	X	X	X	X
178-121*	OB-303	PHEN/TPM	Nervous system disorders	Ischemic stroke	Stroke	X	X	X	X		X
187-037*	OB-302	Placebo	Cardiac disorders	Angina pectoris	NA					X	X
187-037*	OB-302	Placebo	Vascular disorders	Hypertension	NA						X
Subject ID	Study	Treatment	SOC	Preferred Term	Sponsor's Adjudication	CV death, MI, stroke	Ju piter MACE	FDA MACE	Revised FDA MACE	Cardiac disorders SOC SAEs	Cardiovascular or Neurovascular SAE
188-032	OB-303	PHEN/TPM	Cardiac disorders	Myocardial infarction	Myocardial infarction Coronary revascularization	X	X	X	X	X	X
193-032	OB-303	Placebo	Cardiac disorders	Coronary artery disease	Coronary revascularization		X	X	X	X	X
199-037*	OB-303	PHEN/TPM	Cardiac disorders	Acute coronary syndrome	Coronary revascularization		X	X	X	X	X
199-037*	OB-303	PHEN/TPM	Cardiac disorders	Angina pectoris	Hospitalization for unstable angina		X	X	X	X	X
202-003	OB-302	Placebo	Respiratory disorders	Pulmonary embolism	Hospitalization for other cardiovascular causes				X		X

CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction; NA = not applicable; SAE = serious adverse event; SOC = system organ class.
 171-0321 = PHEN/TPM
 * indicates subjects with multiple events



**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: January 20, 2012

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Subject: Review of sponsor's interim report entitled "Fetal outcomes retrospective topiramate exposure study (FORTRESS)."
Dated December 13, 2011

Drug Name(s): Qnexa (phentermine & topiramate)

Submission Number:

Application Type/Number: NDA 22580

Applicant/sponsor: Vivus

OSE RCM #: 2011-4184

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EXECUTIVE SUMMARY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the interim report of the observational study (Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS)) dated December 13, 2011, in support of the New Drug Application (NDA) of Qnexa was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

The FORTRESS study is a retrospective cohort study of the association between topiramate (TPM) and congenital malformations using four data sources (HealthCore, OptumInsight, Kaiser Northern California, and Thomson Reuters). Although the Kaiser Southern California data was proposed in the study protocol, Vivus, the sponsor of Qnexa, clarified that the data from Kaiser Southern California were not available to be included in the study. The interim report provided study results from phase I analyses which addressed the primary study objectives and two secondary objectives based on automated data only.

The preliminary study results provided in this interim report showed that first trimester TPM exposure was associated with about a two-fold (center & propensity score decile-standardized prevalence ratio = 2.45, 95% confidence interval: 0.97-6.18, not statistically significant) increased risk of OCs compared with remote TPM exposure which was at least 120 days prior to the index pregnancy.

The interim report also showed that first trimester TPM exposure was associated with about a six-fold (center & propensity score decile-standardized prevalence ratio = 6.46, 95% confidence interval: 2.07-20.17) increased risk of OCs compared with women with similar medical profiles (SMP) but without TPM exposure in their first trimester of pregnancy. However, the unusually low prevalence of 0.29 OC cases per 1,000 births in the SMP cohort in the HealthCore database suggested that the sampling methods for the SMP cohort might have been problematic or the initial sample was an outlier that occurred by chance. Therefore, the pooled prevalence ratio of OCs for the TPM-exposed cohort vs. the SMP cohort could have been over-estimated. As a result, on January 13, 2012 in response to the sponsor's request to resample the SMP cohort, the FDA requested the sponsor to include all eligible study subjects in the SMP cohort for all study sites to

re-estimate the prevalence ratios. Therefore, the study results in the interim report for comparison of the TPM vs. SMP cohorts are likely to be changed.

(b) (4)

on January 12, 2012, the sponsor informed the FDA that the preliminary analyses for the MCMs were currently undergoing internal quality checks and the results will not be ready to be presented at the AC meeting.

One important study limitation is the limited sample sizes for the subgroup analyses (e.g., TPM high/low dose, short/long duration, monotherapy/polytherapy). Also, the sample size was further reduced in the propensity score stratification analyses. Therefore, depending on what is a clinically acceptable risk, the sample size in the TPM monotherapy subcohort is likely to be inadequate. Another study limitation associated with the use of claims data to identify exposure and outcomes was non-differential misclassification of exposure and outcome. The effect of non-differential misclassification of exposure and outcome usually biases the results toward the null (no association between TPM exposure and outcome). Lastly, this study only investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants and the fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed.

In conclusion, the risks of OCs and MCMs associated with TPM use in the first trimester of pregnancy have not been fully answered in this interim report of the FORTRESS study due to the limited sample size in the TPM monotherapy subcohort, the pending study results using the entire SMP cohort, and the poor data quality issues with the analyses for MCMs.

1 BACKGROUND/HISTORY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the interim report of the observational study (Fetal Outcomes Retrospective Topiramate Exposure Study (FORTRESS)) dated December 13, 2011, in support of the New Drug Application (NDA) for Qnexa was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

Qnexa is a combination of two marketed products, phentermine and topiramate (TPM), for which the applicant is seeking approval for the treatment of obesity and overweight. If approved, Qnexa will be available in three fixed-dose combinations of phentermine/topiramate: 3.75mg/23mg, 7.5mg/46mg, and 15mg/92mg. Recent reports based on the registry data and an observational study from the U.S. and the U.K. have suggested that infants exposed to TPM in utero have an increased risk of oral clefts (OCs) and/or major congenital malformations (MCMs)^{1,2,3}.

A Complete Response letter to Vivus, the sponsor of Qnexa, was issued by FDA on October 28, 2010. An End of Review Conference was held on January 19, 2011, and a follow-up industry meeting was held on April 14, 2011, during which an observational study on the risk of congenital malformations, especially OCs, associated with maternal exposure to TPM during pregnancy was requested by the FDA. A draft study protocol (fetal outcomes retrospective topiramate exposure study (FORTRESS) dated May 25, 2011, was reviewed by DEPI and recommendations were sent to the sponsor. The final study protocol (dated September 6, 2011) and a draft summary pooled analysis plan (dated August 5, 2011) were reviewed by DEPI and recommendations were sent to the sponsor.

The interim report of the FORTRESS study results dated December 13, 2011, was based on the FORTRESS study protocol dated September 6, 2011. The preliminary study results will be discussed in the upcoming Advisory Committee meeting on Qnexa approval on February 22, 2012. On December 19, 2011, FDA requested more study results on the comparison between the TPM monotherapy subcohort and the similar medical profile (SMP) control cohort and study results with data from all data sources included in the analyses. On January 11, 2012, the sponsor responded to FDA's information request and informed FDA that data from the Kaiser Southern California research database were not available to be included in the analyses.

This review will provide an evaluation of the study methods and preliminary results based on data provided in the interim report of the FORTRESS study dated December 13, 2011.

2 REVIEW MATERIALS

Materials that were included in this review are:

- The interim report of the FORTRESS study dated December 13, 2011;
- FORTERESS data development plan (phase 1 final version 4.5) dated November 30, 2011;
- Vivus responses to FDA information request dated January 11, 2012, serial No. 0067.

3 RESULTS OF REVIEW

3.1 STUDY SYNOPSIS

The primary objectives of the FORTRESS study were to estimate the prevalence ratios of oral clefts (OCs) and major congenital malformations (MCMs) in newborns of women exposed to TPM during the first trimester of pregnancy when compared to (a) newborns of women with remote (at least 120 days prior to the index pregnancy) prior exposure to TPM or other antiepileptic drugs (AEDs); and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure. This study was a retrospective cohort study with four data sources (HealthCore, OptumInsight, Kaiser Northern California, and Thomson Reuters). As a result, a total of 1945 mother-baby dyads were included in the TPM-exposed cohorts from these data sources.

The OC prevalence ratios standardized by center were 2.36 (95% CI, 0.99-5.59) for TPM-exposed cohort vs. the formerly exposed (FE) comparison cohort and 5.44 (95% CI, 2.03-14.61) for the TPM cohort vs. the similar medical profile (SMP) comparison cohort. When standardized by propensity score decile and center, the prevalence ratios were 2.45 (0.97-6.18) for TPM vs. FE and 6.46 (2.07-20.17) for TPM vs. SMP. The prevalence ratios standardized by propensity score decile and center were 2.00 (0.71-5.68) for the TPM monotherapy subcohort vs. the FE cohort and 5.71 (1.75-18.58) for the TPM monotherapy subcohort vs the SMP cohort.

(b) (4)

Due to the possibility that the sampling methods of the initial SMP cohort in the HealthCore site may have been problematic or the initial SMP cohort was an outlier occurred by chance, on January 13, 2012, FDA requested the entire SMP cohort for all study sites to be used in the analyses and the results might be provided to FDA later. On January 12, 2012, the sponsor informed the FDA that the preliminary analyses on MCMs was currently undergoing internal quality check and the results in the interim report will not be presented at the AC meeting.

3.2 STUDY OBJECTIVES

3.2.1 Study Objectives:

The primary objectives were:

- 1) to estimate the prevalence ratio of OCs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to: (a) newborns of women with remote (at least 120 days prior to the index pregnancy) prior exposure to TPM or other AEDs (referred to as the FE cohort throughout this review); and (b) newborns of women with medical profiles similar to those in the exposed cohort but with no first trimester TPM exposure (referred to as the SMP cohort throughout this review);
- 2) to estimate the prevalence ratio of MCMs in newborns of women exposed to TPM during the first trimester of pregnancy when compared to: (a) newborns of women in the FE cohort; and (b) newborns of women in the SMP cohort.

The secondary objectives were:

- 1) to estimate the prevalence of OCs and other MCMs in newborns of women exposed to specific doses of TPM during the first trimester and to evaluate any dose response;

- 2) to monitor for any signals of specific MCMs, aside from OCs, associated with TPM exposure in the first trimester;

3.2.2 Reviewer Comments:

The study objectives are appropriate.

3.3 STUDY DESIGN

3.3.1 Study Design:

This study is a retrospective cohort study.

3.3.2 Reviewer Comments:

This reviewer agrees that a retrospective cohort study is appropriate.

3.4 DATA SOURCES

3.4.1 Data Sources:

The final study protocol dated September 6, 2011, proposed to use data from the HealthCore Integrated Research Database (HIRD), OptumInsight Normative Health Information (NHI) database, Kaiser Permanente Northern and Southern California (KPNC & KPSC) Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases.

The HealthCore HIRD database contains longitudinal health claims data on approximately 45 million individuals with medical and pharmacy benefits back to 2001. Medical records can be requested for about 75% of subjects in this database.

The OptumInsight NHI database contains medical and pharmacy claims data from 1994 with a cumulative enrollment of approximately 14 million patients. Medical records can be requested for subjects in a portion of the research database.

The KPNC and KPSC research databases contain automated clinical and pharmacy data that capture live born delivery, diagnoses of malformation, and dispensing of prescription medications. More than 3.3 million members are served by the KPNC and a similarly sized population is served by KPSC.

The Thomson Reuters MarketScan Multi-State Medicaid Research Database contains healthcare service use of individuals covered by Medicaid programs in several

geographically dispersed states. The Multi-State Medicaid database dates back to 1999 and contains an average of 10 million Medicaid enrollees each year.

3.4.2 Reviewer Comments:

The proposed use of the HealthCore HIRD database, OptumInsight NHI database, KPNC and KPSC Research Databases, and the Thomson Reuters MarketScan Multi-State Medicaid Research Databases is acceptable. However, this interim report did not list the Kaiser Northern California as one of the data sources. As the FDA requested the sponsor to include the Kaiser Northern California data into all analyses, the sponsor responded that “The Kaiser Permanente data included in the interim report dated December 13, 2011 came exclusively from Kaiser Permanente of Northern California. The interim report inadvertently misidentified this data as having come from Kaiser Permanente of Southern California. No data from Kaiser Permanente of Southern California was used in the Fortress study.”

3.5 STUDY POPULATION

3.5.1 Proposed Study Population:

The study population included women with a record of live birth during the study period and an identifiable newborn with at least 90-day post-delivery enrollment. Women eligible to enroll in this study included those who: 1) had at least 6 months of continuous enrollment in the health plan prior to the presumed conception date, and 2) were between the ages of 15 and 49 years on the delivery date.

Women were excluded if they had: 1) a history of infection with one of the TORCH agents (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis, varicella-zoster, and parvovirus B19), 2) a history of alcohol abuse or substance abuse, or 3) an exposure to thalidomide or isotretinoin during the 6 months preceding the presumed conception date or at any point during the pregnancy.

3.5.2 Reviewer Comments:

The reviewer agrees that the study population and the inclusion/exclusion criteria are appropriate.

3.6 EXPOSURES

3.6.1 Exposures:

A Mother-baby pair exposed to TPM during the first trimester of pregnancy was defined as those for whom prescription data indicate exposure to TPM at any dose during the first trimester. Exposure to TPM or other AEDs was ascertained using National Drug Codes (NDCs) from prescription claims data. A woman was considered exposed if TPM was dispensed during the exposure window (defined in the next paragraph in this Section) or if an earlier dispensing included enough supply to carry over into the exposure period. Exposure to TPM was defined in two ways: 1) as an indicator variable for whether there was first trimester exposure; and 2) as a numerical variable based on calculated average daily dose.

The exposure window of the first trimester was defined as: 1) for women who delivered at term, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 287 through 168 days before delivery for singleton births or from 273 through 147 days before delivery for multiple births (note: multiple births are usually delivered earlier than single births); 2) for women with a diagnosis code of premature delivery and the length of gestation is not specified, the earliest possible date of conception through 91 days following the latest possible date of conception, or from 252 through 133 days before delivery; and 3) for those with some delivery codes indicating length of gestation, as the first 91 days of the specified gestation period.

For the FE comparison cohort of mother-infant pairs with remote prior exposure to TPM or any other AEDs before the index pregnancy, eligible cohort members were those exposed to TPM or other AEDs from the earliest continuous enrollment up to 120 days before the estimated earliest conception period for the index pregnancy. This cohort excluded mothers who were exposed to TPM or other AEDs during the pregnancy or within 120 days before the estimated conception date.

The SMP comparison cohort consisted of mothers with similar medical profiles as the TPM cohort (seizure/epilepsy, migraine, or other), but without current exposure to TPM during pregnancy or during the 120 days prior to the earliest conception date. The SMP cohort did not contain any mothers without a history of seizure/epilepsy, migraine,

or other TPM indication. The SMP cohort was frequency matched to the TPM-exposed cohort at a 7:1 ratio by indication. Members of the SMP cohort may also be included in the FE cohort.

3.6.2 Reviewer Comments:

This reviewer agrees that the definitions of exposure and exposure window are appropriate.

3.7 DISEASE OUTCOMES OF INTEREST

3.7.1 Proposed Study Outcomes:

Primary Outcomes:

One of the primary outcomes was nonsyndromic OCs that are not associated with diagnosed or suspected chromosomal or genetic defects. OCs were identified using ICD-9-CM diagnosis codes or CPT procedure codes associated with claims for physician services or hospitalization that occur within 30 days of the presumed delivery date on the mother's claims or within 365 days of birth date on the infant's claims. Mother-infant pairs who had additional claims data suggesting syndromic malformations or genetic or chromosomal defects did not qualify as cases.

The other primary outcomes were MCMs which were defined as conditions present at birth resulting from malformation, deformation, or disruption in one or more parts of the body and having serious adverse effects on the health, development, or functional ability. MCMs were identified using ICD-9-CM diagnosis codes within 30 days of the delivery date on the mother's claims or within 365 days of birth date on the infant's claim. Mother-infant pairs who have additional claims data suggesting syndromic malformations or genetic or chromosomal defects did not qualify as cases.

Secondary Outcomes:

Specific MCMs other than OCs (not pre-specified) were explored as secondary endpoints.

3.7.2 Reviewer Comments:

The primary outcomes of OCs and MCMs in this interim report were based on the claims data only and no validation effort was undertaken. Therefore, the study results should be considered as preliminary only.

3.8 STUDY COVARIATES

3.8.1 Study Covariates

Potential confounders that were evaluated in the stratified analyses included maternal age, indications for TPM use, maternal diabetes, exposure to known or suspected teratogens, geographic area, race/ethnicity, infant sex, delivery type (single/multiple birth), and premature birth. Each potential confounder was evaluated one at a time by comparing results standardized by center with results that were standardized by center and one potential confounder. A change of less than 10% in the prevalence ratio was used as an indicator that confounding for that variable was of negligible importance.

These study covariates listed above and other potential confounders (maternal conditions of seizures/epilepsy, migraine, schizophrenia, episodic mood disorders, anxiety disorders, chronic pain, obesity, and hypertension; medications of valproate, carbamazepine, phenytoin, Phenobarbital, other AEDs, folic acid antagonists, other teratogens; maternal smoking, and calendar year based on the earliest date of conception) were also controlled simultaneously by center-specific propensity score decile.

3.8.2 Reviewer Comments:

These study covariates and the evaluations of confounding are appropriate based on previous studies in the literature^{3,4}. It would be more complete if the study could have also evaluated the study covariates of maternal alcohol use, maternal and family history of MCMs, and mother's parity. However, this reviewer agrees that it is not feasible to evaluate these variables in this study.

3.9 SAMPLE SIZE

3.9.1 Sample Size

A total of 1,945 mother-baby dyads who had exposure to TPM during their first trimester of pregnancy were included in the TPM-exposed cohort. A total of 13,512

mother-infant pairs were included in the FE comparison cohort and 13,614 mother-infant pairs were included in the SMP comparison cohort.

3.9.2 Reviewer Comments:

The sample size in the TPM-exposed cohort was reduced from the estimated 2,300 to 1,945 in the interim analyses. The sample size in the SMP comparison cohort was reduced from the estimated 16,100 to 13,614 (TPM: SMP ratio of 1:7). The sample size in the FE control cohort was increased from the estimated 10,000 to 13,512 (TPM: FE ratio of 1:7). Based on the previous power calculations performed by the FDA's Office of Biostatistics (Table 1), the smallest possible relative risk (RR) that could be ruled out with 80% power should be within the range of 3.40-4.47 for OCs and within the range of 1.31-1.40 for MCMs given the study size in the interim analyses. However, the sample sizes for the subgroup analyses (e.g., TPM high/low dose, short/long duration, monotherapy/polytherapy) were more limited. Also, the sample size was further reduced in the propensity score stratification analyses. Therefore, depending on what is a clinically acceptable risk, the sample size in the TPM monotherapy subcohort is likely to be inadequate.

Table 1: Estimates of the smallest possible RR that could be ruled out under the study size and power restrictions and the associated number of excess events above the background rate (data source: Statistical review, Office of Biostatistics, FDA)

TPM-Exposed Dyads	Control Cohort	Power	Oral Clefts		MCMs	
			Rule Out RR of	Excess Events*	Rule Out RR of	Excess Events*
1,400	9,800 (ratio of 1:7)	80%	4.47	4.2	1.40	10.0
2,200	15,400 (ratio of 1:7)	80%	3.40	2.9	1.31	7.9

* Excess events in number of events per 1,000 patients above the background rate of 1.2 events per 1,000 (for OCs) or 25 events per 1,000 (for MCMs)

3.10 ANALYSES

3.10.1 Proposed Analyses

Descriptive statistics were computed for demographic variables and relevant covariates and summarized within each database. Prevalence estimates of OCs and other MCMs were computed in each database.

In the main analyses & pooled analysis for prevalence ratios of OCs and MCMs, stratified analyses were conducted within each data source. The stratified tables were forwarded to RTI Health Solutions for the final pooled analysis, which also involved stratification by study center. Summary prevalence ratio estimates standardized to the TPM-exposed cohort were reported.

A second approach involved stratification by propensity score deciles calculated within each data source. The variables that were included to generate propensity scores include maternal age, infant sex, calendar year, geographic region, smoking, use of valproate, carbamazepine, phenytoin, other AEDs, folic acid antagonists, known or suspected teratogens, history of epilepsy, migraine, affective disorder, diabetes, hypertension, and obesity. Strata of propensity score were defined by deciles of the propensity score distribution.

Two secondary analyses were conducted to assess: 1) the dose-response relationship by estimating the effect of 100 mg or less per day versus more than 100 mg per day of TPM during the first trimester; 2) the duration-response relationship by evaluating whether the TPM effect varies according to the number of exposed days within the first trimester.

An exploratory study was conducted to assess the presence of signals for increased risks of MCMs by organ system affected. The main outcome was the prevalence ratio of organ system-specific MCMs among women with first trimester exposure to TPM when compared to the control groups.

3.10.2 Reviewer Comment:

Because of the low count of OC cases in each study site and the large number of potential confounding factors that need to be controlled, the propensity score approach is

the preferred method versus the covariate-based stratified analysis. The strata in the propensity score approach should be classified by quartiles instead of deciles of propensity score distribution to minimize the zero or low count problem associated with stratification by deciles. The distributions of study covariates within each stratum (propensity score quartiles) should be provided to the FDA to examine whether these covariates were balanced across study cohorts. Also, infant sex should not be included in the logistic regression model to generate propensity scores as this is not a factor affecting the probability of each mother using TPM during early pregnancy.

Due to the limited sample size and rare outcomes, some of the subgroup analyses may not be able to provide stable estimates and the results could be difficult to interpret.

3.11 STUDY RESULTS

3.11.1 Study Results

The number of OC cases in each study center was very small. A summary of the number of OC cases and characteristics of each cohort, stratified by center were presented in Table 1.

Table 2. Sample size, number of OC cases, and patient characteristics by study cohort and by center

Characteristics	Topiramate (TPM) Cohort (n=1,945)	Formerly Exposed (FE) Cohort (n=13,512)	Similar Medical Profile (SMP) Cohort (n=13,614)
Number of infants			
HealthCore	495	2,935	3,465
Kaiser	119	2,044	833
OptumInsight	748	4,196	5,235
Thomson Reuters	583	4,337	4,081
Number of OC cases (prevalence per 1,000 births)			
HealthCore	3 (6.06)	3 (1.02)	1 (0.29)
Kaiser	0 (0.00)	4 (1.96)	0 (0.00)
OptumInsight	3 (4.01)	8 (1.91)	4 (0.76)
Thomson Reuters	1 (1.72)	6 (1.38)	4 (0.98)
Percentage with maternal characteristic			
Caucasian race			

Characteristics	Topiramate (TPM) Cohort (n=1,945)	Formerly Exposed (FE) Cohort (n=13,512)	Similar Medical Profile (SMP) Cohort (n=13,614)
HealthCore	NA	NA	NA
Kaiser	59	53	48
OptumInsight	83	82	79
Thomson Reuters	80	65	69
Epilepsy indication			
HealthCore	11	7	12
Kaiser	17	9	17
OptumInsight	11	7	11
Thomson Reuters	18	13	19
Migraine indication			
HealthCore	66	36	73
Kaiser	66	34	67
OptumInsight	66	43	69
Thomson Reuters	43	21	46
Premature birth			
HealthCore	11	11	9
Kaiser	13	12	9
OptumInsight	11	11	9
Thomson Reuters	9	11	10
Diabetes			
HealthCore	6	5	4
Kaiser	8	5	4
OptumInsight	5	6	5
Thomson Reuters	7	5	4
Hypertension			
HealthCore	6	4	4
Kaiser	7	4	4
OptumInsight	7	5	4
Thomson Reuters	9	5	6
Obesity			
HealthCore	2	1	1
Kaiser	39	29	24
OptumInsight	11	9	8
Thomson Reuters	12	10	13
Exposure to possible teratogen during first trimester			
HealthCore	21	16	12

Characteristics	Topiramate (TPM) Cohort (n=1,945)	Formerly Exposed (FE) Cohort (n=13,512)	Similar Medical Profile (SMP) Cohort (n=13,614)
Kaiser	15	7	11
OptumInsight	19	15	14
Thomson Reuters	32	18	21
AED poly-exposures			
HealthCore	8	0 ^a	<1
Kaiser	11	0 ^a	2
OptumInsight	7	0 ^a	1
Thomson Reuters	16	0 ^a	1

^a By definition, no antiepileptic drug (AED) therapy during pregnancy.

As shown in Table 3, the OC prevalence ratio for the TPM-exposed cohort vs. FE comparison cohort standardized by center was 2.36 (95% CI, 0.99-5.59). The center-standardized OC prevalence ratio for TPM cohort vs. the similar medical profile (SMP) comparison cohort was 5.44 (95% CI, 2.03-14.61). When standardized by propensity score and center, the prevalence ratios were 2.45 (0.97-6.18) for TPM vs. FE and 6.46 (2.07-20.17) for TPM vs. SMP.

The sponsor claimed in the interim report that the birth prevalence of 0.29 OC cases per 1,000 births in the SMP cohort at HealthCore seemed unusually low. HealthCore repeated the sampling process 1,000 more times, using the same sample size to assess the extent to which the initially reported prevalence based on one case was a chance outlier. Across the 1,000 samples, both the mean and the mode were 5 cases observed (a prevalence of 1.44 cases per 1,000 births). Among the 1,000 samples, 3% were observed with one or fewer OC cases. Therefore, the sponsor stated that comparison with the FE cohort, but not the SMP cohort, provided the most reliable estimate. Originally, the interim report only reported the prevalence ratios for the TPM monotherapy subcohort vs. the FE cohort. Upon FDA request, the prevalence ratios for the TPM monotherapy subcohort vs. the SMP cohort were provided which were presented in Table 4.

Table 3. Standardized prevalence ratios of OCs for TPM-exposed cohort compared with the FE and the SMP control cohorts

Standardization Variables	PR of TPM vs. FE	95% CI	PR of TPM vs. SMP	95% CI
Crude	2.32	0.99-5.44	5.44	2.03-14.60
Study center	2.36	0.99-5.59	5.44	2.03-14.61
Age & center	2.52	1.06-6.00	5.86	2.17-15.81
Region & center	2.57	1.08-6.11	5.25	1.93-14.27
Diabetes & center	2.38	1.00-5.66	5.09	1.87-13.82
Teratogenic drug exposure & center	2.37	0.99-5.65	6.05	2.25-16.23
TPM indication & center	2.10	0.86-5.12	6.30	2.34-16.96
Race/ethnicity & center	2.37	1.00-5.64	5.52	2.00-15.26
Infant sex & center	2.33	0.98-5.53	5.47	2.04-14.67
Delivery type & center	2.30	0.97-5.47	5.35	1.99-14.35
Premature birth & center	2.34	0.99-5.55	5.50	2.05-14.74
Propensity score & center	2.45	0.97-6.18	6.46	2.07-20.17

Table 4. Prevalence ratios of OCs standardized by propensity score decile and center for TPM monotherapy compared with the FE and SMP cohorts by TPM dose and duration

Exposure Category	PR of TPM vs. FE	95% CI	PR of TPM vs. SMP	95% CI
Overall	2.00	0.71-5.68	5.71	1.75-18.58
TPM low dose*	2.12	0.60-7.56	5.75	1.44-22.93
TPM high dose**	1.85	0.41-8.26	5.65	1.14-27.91
TPM short duration of therapy***	1.67	0.37-7.49	4.65	0.94-23.04
TPM long duration of therapy****	2.31	0.65-8.23	6.74	1.68-27.08

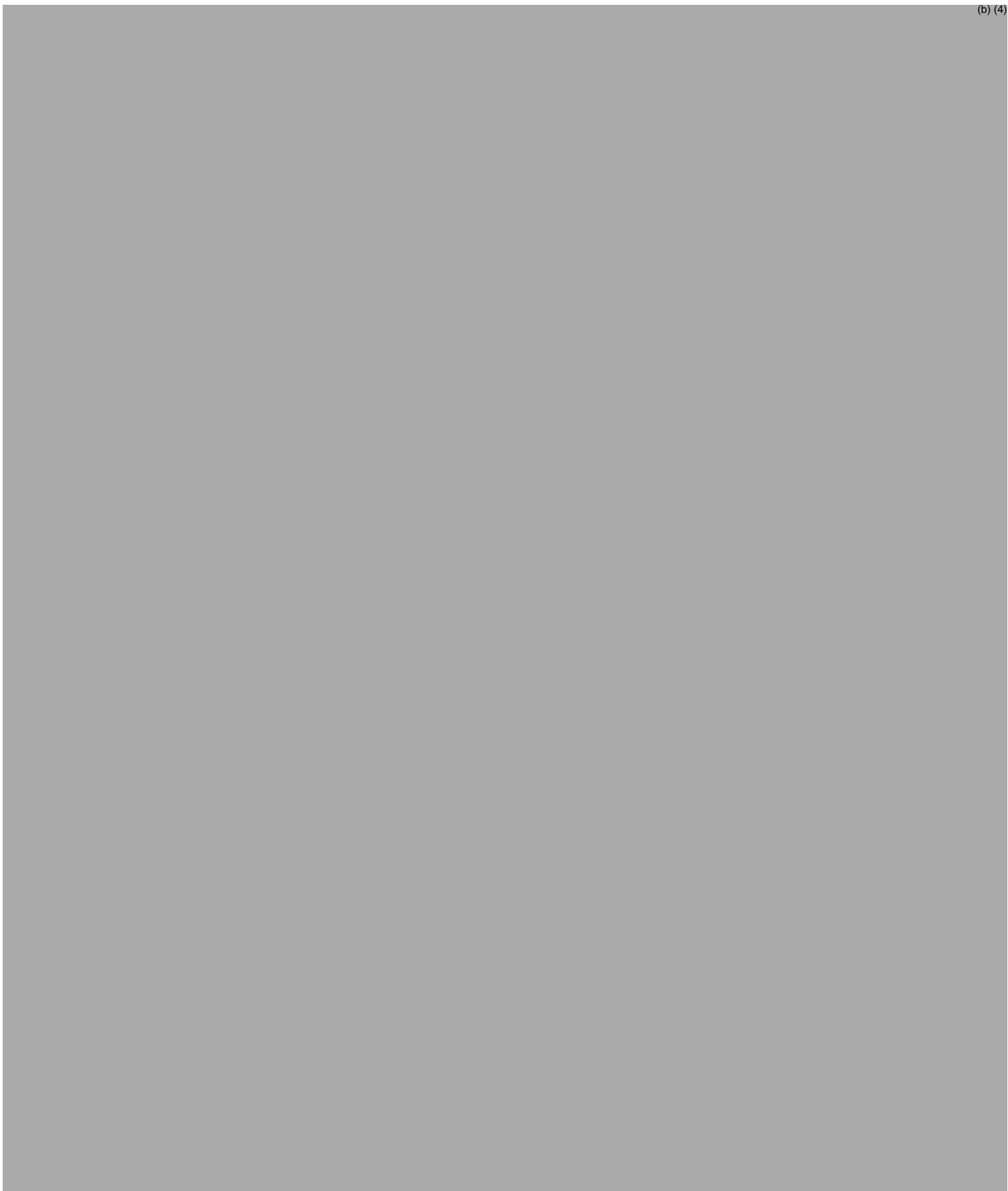
* low-dose: daily TPM doses of 100 mg or less

** high-dose: daily TPM doses greater than 100 mg

***short-duration: equal or less than 38 days, 38 days, 51 days, or 43 days of TPM use during the first trimester in data sites of HealthCore, OptumInsight, Kaiser, Thomson Reuters, respectively

****long-duration: more than 38 days, 38 days, 51 days, or 43 days of TPM use during the first trimester in data sites of HealthCore, OptumInsight, Kaiser, Thomson Reuters, respectively

(b) (4)



3.11.2 Reviewer Comment:

As the propensity score stratification is the preferred method over the covariate-based stratified analysis, this review will focus on the prevalence ratios standardized by propensity score decile and center. For the TPM-exposed cohort vs. FE control cohort, the propensity score and center-standardized prevalence ratio was 2.45 (0.97-6.18), which suggests that first trimester TPM exposure was associated with about a two-fold increased risk of OCs compared with remote TPM exposure which was at least 120 days prior to the index pregnancy. For the TPM-exposed cohort vs. the SMP control cohort, the propensity score and center-standardized prevalence ratio was 6.46 (2.07-20.17), which suggests that first trimester TPM exposure was associated with about a six-fold increased risk of OCs compared to no TPM exposure in the first trimester of pregnancy.

The investigation from the HealthCore study site into the sampling of their SMP cohort suggested that the initial selected SMP cohort might be a statistical aberration, capturing only 1 case of OC, whereas upon repeated samples the mean was 5 cases of OCs. DEPI agrees that this initial sampling of SMP cohort in the HealthCore data could be an outlier occurred by chance or the sampling method for the SMP cohort could be problematic and the prevalence ratios for the TPM vs. SMP cohorts could have been over-estimated.

The sponsor raised a question about resampling the SMP cohort at all study sites. Recognizing that the original sampling of the SMP cohort in the HealthCore site could be an outlier by chance, resampling the SMP cohort in the HealthCore site alone might be acceptable under certain conditions. However, the analyses would be considered post-hoc using the re-sampled SMP cohort and the study results could be manipulated by picking a favorable SMP sample. To minimize the potential bias, DEPI suggests that the sponsor use all eligible study subjects from the SMP control cohort at all study sites to re-assess the prevalence ratios of OCs and MCMs.

This reviewer disagrees with the sponsor's claim that the FE cohort offers a more valid comparison than the SMP cohort. The prevalence ratios using different comparison

cohorts, FE & SMP, provide different information and should be interpreted accordingly. The comparison with the FE cohort would inform whether the timing of exposure matters in the development of OCs. The risk estimates using the SMP comparison cohort would inform whether first-trimester TPM exposure was associated with an increased risk of OCs controlling for underlying conditions (TPM indications). Therefore, it is important to provide the risk estimates using the SMP comparison cohort in the FORTRESS Study.

One important limitation of the interim analyses is the misclassification bias. As the study investigators pointed out that the use of claims data to identify exposure and outcomes has certainly introduced some, presumably non-differential misclassification bias. The effect of non-differential misclassification of exposure and outcome usually biases the results toward the null (no association between TPM exposure and outcome).

4 SUMMARY

The study results from this interim report were based on claims-only analyses without validation effort and would be considered preliminary. The preliminary study results showed that first trimester TPM exposure was associated with about a two-fold (not statistically significant) increased risk of OCs compared with remote TPM exposure which was at least 120 days prior to the index pregnancy.

Data from the interim report also showed that first trimester TPM exposure was associated with about a six-fold increased risk of OCs compared to no TPM exposure in their first trimester of pregnancy. However, the unusually low prevalence of 0.29 OC cases per 1,000 births in the SMP cohort at the HealthCore site suggested that the sampling methods for the SMP cohort may have been problematic or the initial sample was a chance outlier. Therefore, the pooled prevalence ratio of OCs for the TPM-exposed cohort vs. the SMP cohort could have been over-estimated. FDA has requested the sponsor to use all eligible study subjects in the SMP cohort for all study sites to re-estimate the prevalence ratios and the results are likely to be changed.

(b) (4)

This reviewer disagrees with the sponsor's claim that the FE cohort offers a more valid comparison than the SMP cohort. The prevalence ratios using different comparison cohorts, FE & SMP, provide different information and should be interpreted accordingly. The comparison with the FE cohort would inform whether the timing of exposure matters in terms of OC risk. The risk estimates using the SMP comparison cohort is as important as these estimates would inform whether the first-trimester TPM exposure is associated with an increased risk of OCs controlling for underlying conditions (TPM indications). Therefore, the FORTRESS study should use all eligible study subjects in the SMP cohorts at all study sites to re-assess the prevalence ratios of OCs and MCMs and provide the study results to the FDA for evaluation.

One important study limitation is the limited sample sizes for the subgroup analyses (e.g., TPM high/low dose, short/long duration, monotherapy/polytherapy). Also, the sample size would be further reduced in the propensity score stratification analyses. Therefore, depending on what is a clinically acceptable risk, the sample size in the TPM monotherapy subcohort is likely to be inadequate. Another study limitation associated with the use of claims data to identify exposure and outcomes was non-differential misclassification of exposure and outcome. The effect of non-differential misclassification of exposure and outcome usually biases the results toward the null (no association between TPM exposure and outcome). Lastly, this study only investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants and the fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed.

In conclusion, the risks of OCs and MCMs associated with TPM use in the first trimester of pregnancy have not been fully answered in this interim report of the FORTRESS study due to the limited sample size in the TPM monotherapy subcohort, the pending study results using the entire SMP cohort, and the poor data quality issues with the analyses for MCMs.

5 RECOMMENDATIONS TO BE SENT TO THE SPONSOR

- *Please obtain more mother-baby dyads for the FORTRESS study (e.g. from the Kaiser Southern California research database as proposed in the study protocol) to ensure an adequate sample size in the TPM monotherapy subcohort.*
- *Please re-assess the prevalence ratios of OCs and MCMs using all eligible study subjects in the SMP cohorts at all study sites and submit study results to the FDA.*
- *Please provide data on the distributions of study covariates within each stratum with the propensity score stratification approach to the FDA to examine whether these covariates were balanced across study cohorts.*
- *Please incorporate FDA's recommendations (including the following three sub-bullets) regarding the study protocol (dated September 6, 2011) and the draft summary pooled analysis plan (dated August 5, 2011) into the study.*
 - *You should validate all potential MCM cases that will be identified in the study cohorts. Alternatively, the sponsor may restrict the validation to all of the 10 most common specific MCMs. The validation should be done in the study cohorts to enhance the validity of the study results and only validated cases should be included in the final analyses. The PPV should be estimated using both the base case definition and the secondary, more restrictive case definition. A sampling approach is not preferred because of the challenges of specifying appropriate sampling fraction and acceptable precision margins for PPV given the heterogeneity of malformations. Additionally, low PPV values present a challenge in utilizing the validation data in estimating the risk.*
 - *The propensity score stratification analysis is preferred over the stratified analysis by individual covariate and the strata should be classified by quartiles instead of deciles of propensity score distribution. A sensitivity analysis using propensity score matching should be performed.*

- *Infant sex should not be included in the logistic regression model to generate propensity scores as this is not a factor affecting the probability of a mother using TPM during early pregnancy*

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¹ Holmes LB, Hernandez-Diaz S, Shen A, et al. Registry releases topiramate findings: increased risk for malformations and low birth weight. The North American Antiepileptic Drug Pregnancy Registry. 2011.

² Kennedy F, Morrow J, Hunt S, et al. PATH39 malformation risks of antiepileptic drugs in pregnancy: an update from the UK epilepsy and pregnancy register. J Neurol neurosurg Psychiatry. 2010; 81(11): e18.

³ Margulis AV, Werler MM, Mitchell AA, et al. Use of Topiramate in Pregnancy and the Risk of Oral Clefts. Abstracts of the 27th ICPE 2011.

⁴ Molgaard-Nielsen, D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. JAMA. 2011; 305(19): 1996-2002.

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01/20/2012

TAREK A HAMMAD
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**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: January 20, 2012

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Subject: Addendum to Review of sponsor's Qnexa teratogenicity
report entitled "Clinical review of topiramate and PHEN/TPM
teratogenic potential" dated September 27, 2011

Drug Name(s): Qnexa (phentermine & topiramate)

Submission Number:

Application Type/Number: NDA 22580

Applicant/sponsor: Vivus

OSE RCM #: 2011-4184

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EXECUTIVE SUMMARY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP) in preparation for the Advisory Committee meeting on February 22, 2012, the Qnexa teratogenicity report entitled “Clinical review of topiramate and PHEN/TPM teratogenic potential” dated September 27, 2011, and three abstracts/posters that were cited in this report were reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

In summary, each of the three studies has limitations, but with different directions of bias and significance. All three investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants. The fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed. Overall, the Slone/CDC study provided more reliable risk estimates of oral clefts (OCs) associated with TPM exposure during the first trimester of pregnancy compared to the other two studies. The risks of OCs and major congenital malformations (MCMs) were probably underestimated in the Wolters Kluwer study because most of the study limitations would bias the results towards no association between TPM exposure and risk of OCs. The sponsor’s comment that the Denmark study confirms an absence of a signal for an increased prevalence of MCMs with topiramate exposure is not supported because of the limited statistical power of the Denmark study.

1 BACKGROUND/HISTORY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), the Qnexa teratogenicity report entitled “Clinical review of topiramate and PHEN/TPM teratogenic potential” dated September 27, 2011, and three abstracts/posters that were cited in this report were reviewed by the Division of Epidemiology I (DEPI I) in the Office of Pharmacovigilance and Epidemiology (OPE).

Qnexa is a combination of two marketed products, phentermine and topiramate (TPM), for which the applicant is seeking approval for the treatment of obesity and overweight. If approved, Qnexa will be available in three fixed-dose combinations of phentermine/topiramate: 3.75mg/23mg, 7.5mg/46mg, and 15mg/92mg. Recent reports based on registry data from the U.S. and the U.K. have suggested that infants exposed to

topiramate (TPM) in utero have an increased risk of oral clefts (OCs) and major congenital malformations (MCMs).^{1,2,3}

This review will comment on the methodologies, study results, and strengths and limitations of the three studies. DEPI will also provide possible reasons for the differences in results between the Slone/CDC and the Wolters Kluwer studies based on limited information available from the abstracts, posters, and the Qnexa teratogenicity report. Finally we will comment on the sponsor's statement that the Denmark study confirms an absence of a signal for increased prevalence of MCMs with TPM exposure.

2 REVIEW MATERIALS

Materials that were included in this review are:

- A published cohort study by Molgaard-Nielsen (referred throughout this review as the Denmark Study)⁴;
- A study abstract by Margulis et al. that was presented at the 27th ICPE meeting (referred throughout this review as the Slone/CDC study)³;
- An abstract and poster of a part of a study funded by the sponsor using the Wolters Kluwer Pharma Solutions data by Green et al. that was presented at the 136th Annual meeting of the American Neurological Association (referred throughout this review as the Wolters Kluwer study)⁵;
- An abstract and poster of a different part of the study funded by the sponsor using the Wolters Kluwer Pharma Solutions data by Pack et al. that was presented at the 29th International Epilepsy Congress (referred throughout this review as the Wolters Kluwer study)⁶; and
- The Qnexa teratogenicity report entitled “Clinical review of topiramate and PHEN/TPM teratogenic potential” dated September 27, 2011.

3 RESULTS OF REVIEW

3.1 STUDY SYNOPSIS

3.1.1 Slone/CDC Study

Data from two case-control surveillance programs in North America, the Slone Epidemiology Center Birth Defects Study (BDS, 1997-2009) and the Center for Disease Control's National Birth Defects Prevention Study (NBDPS, 1996-2007) were analyzed to examine the association between the use of TPM in pregnancy and the risk of cleft lip with or without cleft palate and isolated cleft palate. Logistic regression models were used to compare first trimester use of TPM monotherapy vs. no use of antiepileptics between cases and non-malformed controls matched on year and region of birth. The median daily dose of TPM was 100 mg for both cases and controls (range: 25-150 mg). The odds ratio (OR) for MCMs was 1.22 (95% CI, 0.19-13.01) in the Slone data and 0.92 (95% CI, 0.26-4.06) in the CDC data; for cleft lip with or without cleft palate, the OR was 10.13 (95% CI, 1.09-129.21) in the Slone data and 3.63 (95% CI, 0.66-20.00) in the CDC data. The pooled OR was 1.01 (95% CI, 0.37-3.22) for MCM and 5.36 (95% CI, 1.49-20.07) for cleft lip with or without cleft palate. There was no case of isolated cleft palate in TPM-exposed pregnancies. The study concluded that first-trimester use of TPM monotherapy may be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate or overall MCMs.

3.1.2 Wolters Kluwer Study

A retrospective cohort study sponsored by Vivus used data from Wolters Kluwer Pharma Solutions Source LX Patient longitudinal datasets (January 2003 – December 2010) from the United States to examine the risk of MCMs, including OCs, among infants exposed to TPM in utero anytime during pregnancy (n=910) and during the first trimester only (n=870). Five control cohorts were comprised of:

- 1) Women exposed to other antiepileptic drugs (AEDs) during the first trimester of pregnancy (n=3,615);
- 2) Women with a diagnosis of epilepsy but without TPM exposure (n=2,607);
- 3) Women with a diagnosis of migraine but no diagnosis of epilepsy and not treated during pregnancy with acute and preventive migraine drugs (n=26,865);

4) Women with a diagnosis of migraine but no diagnosis of epilepsy and treated during pregnancy with acute and preventive migraine drugs (n=2,526); and

5) Women with a diagnosis of diabetes other than gestational (n=13,063).

The relative risks (RR) of MCMs were:

- 1.33 (95% CI, 0.92-1.90) for TPM vs. other AEDs
- 0.98 (95% CI, 0.68-1.41) for TPM vs. the epilepsy control group
- 1.12 (95% CI, 0.81-1.55) for TPM vs. migraine control group
- 0.99 (95% CI, 0.68-1.42) for TPM vs. treated migraine control group
- 0.65 (95% CI, 0.47-0.89) for TPM vs. the diabetes control group

The RRs of OCs were:

- 1.39 (95% CI, 0.28-6.85) for TPM vs. other AEDs
- 0.88 (95% CI, 0.18-4.21) for TPM vs. the epilepsy control group
- 1.47 (95% CI, 0.36-6.06) for TPM vs. migraine control group
- 0.95 (95% CI, 0.19-4.68) for TPM vs. treated migraine control group
- and 0.88 (95% CI, 0.21-3.67) for TPM vs. the diabetes control group

This study concluded that there was no significantly increased risk of OCs or MCMs associated with TPM exposure during the first trimester of pregnancy or anytime during pregnancy.

3.1.3 Denmark Study

A population-based cohort study in Denmark examined the association between fetal exposure to newer-generation AEDs (lamotrigine, oxcarbazepine, topiramate, gabapentin, levetiracetam) during the first trimester of pregnancy and the risk of major birth defects from January 1, 1996, through September 30, 2008. A major birth defect was diagnosed in 5 out of 108 infants exposed to TPM compared with 19,911 out of 836,263 infants with no exposure to any of the newer-generation AEDs. The adjusted prevalence odds ratio of major birth defect was 1.44 (95% CI, 0.58-3.58) for TPM exposure vs. unexposed to any newer-generation AEDs. The study concluded that first-trimester exposure to newer-generation AEDs compared with no exposure was not associated with an increased risk of major birth defects.

3.2 STUDY ELEMENTS & DEPI COMMENTS

3.2.1 Study Objectives

3.2.1.1 Study Objectives:

Slone/CDC study:

- To evaluate the association between the use of TPM in the first trimester of pregnancy and the risk of cleft lip with or without cleft palate and isolated cleft palate

Wolters Kluwer study:

- To examine the risk of MCMs and OCs, among infants exposed to TPM in utero compared to controls

Denmark study:

- To study the association between fetal exposure to newer-generation antiepileptic drugs (AEDs) during the first trimester of pregnancy and the risk of major birth defects

3.2.1.2 Reviewer Comments:

Both the Slone/CDC and the Wolters Kluwer studies examined the effect of TPM exposure during pregnancy, while the Denmark study examined the combined effect of newer-generation AEDs. The Denmark study was not powered to examine the individual effect of TPM exposure. The primary study outcome for both the Slone/CDC and the Wolters Kluwer study was OCs. However, the primary outcome for the Denmark study was MCMs.

3.2.2 Study Design

3.2.2.1 Study Design:

Slone/CDC study:

- A pooled case-control study (consisting of two separate case-control studies, one from the Slone Epidemiology Center and the other from CDC)

Wolters Kluwer study:

- A retrospective cohort study

Denmark study:

- A retrospective cohort study

3.2.2.2 Reviewer Comments:

An observational cohort study can be advantageous over a case-control study when it comes to recall bias which is often associated with case-control studies. Since controls were non-malformed infants in the Slone/CDC study, a differential recall bias may exist between cases and controls in reporting drug exposure, including TPM exposure, during the first trimester of pregnancy.

Since the study outcome of OCs are rare and the exposure is limited, a case-control study can be a very efficient study design. A cohort study, on the other hand, may suffer from inadequate sample size and study power, which is unfortunately the case for the Wolters Kluwer study and the Demark study.

3.2.3 Data Sources

3.2.3.1 Data Sources:

Slone/CDC study:

- The Slone Epidemiology Center Birth Defects Study (BDS), 1997-2009
- The Center for Disease Control's National Birth Defects Prevention Study (NBDPS), 1996-2007

The Slone Epidemiology Center is a public health research organization focusing on studying the possible health effects of medications in adults and children. The Birth Defects Study (BDS) is a case-control birth defects study spanning over 25 years that assesses the risks of birth defects in relation to medications taken during pregnancy. The database currently has information on over 32,700 mother-child pairs.

The National Birth Defects Prevention Study (NBDPS) is a population-based, case-control study examining the risk factors and potential causes of birth defects with data collection since 1997. The Centers for Disease Control and Prevention (CDC)

coordinated the NBDPS, which is a collaborated study by ten study centers (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Women whose babies have birth defects were invited to participate in the study. Women whose babies do not have birth defects were selected randomly from women who gave birth in the same area during the same year. Phone interviews are conducted to collect information on past pregnancies, health and diet, prescription and non-prescription drugs, work and hobbies, lifestyle, and father's work and lifestyle. Genetic data are collected from cheek cells from mothers, fathers, and babies.

Wolters Kluwer study:

- The Wolters Kluwer Pharma Solutions Source Lx Patient longitudinal data, January 2003 – December 2010

The Wolters Kluwer Source Lx Patient database is a longitudinal patient data source which captures adjudicated prescription and medical claims across the United States from commercial plans, cash payments, Medicare Part D plans, and Medicaid claims. Source Lx Patient data contains information on patient age and gender, prescriber specialty and geography, prescriptions, diagnoses, and procedures. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics and outpatient facilities, and 80,000 physician practices. Patients in Source Lx are distributed proportionally to the 2009 U.S. Census in the Northeast and Southern Census regions. However, the population is underrepresented in the Midwest and overrepresented in the West.

Denmark study:

- The Medical Birth Registry in Denmark, January 1, 1996 – September 30, 2008
- The Registry of Medicinal Product Statistics in Denmark (time frame not provided)
- The National Patient Registry in Denmark, January 1, 1996 – March 31, 2009

A study cohort of all live births from January 1, 1996, through September 30, 2008 was constructed using the Medical Birth Registry. The Medical Birth Registry contains records on all Danish births, which include the personal identification numbers

of the parents and the newborn, date of birth, indication of single vs. multiple births, gestational age, vital status, and other physical characteristics of the newborn.

Exposure to AEDs was obtained from the Registry of Medicinal Product Statistics, which contains patient-level data on all prescriptions dispensed at Danish pharmacies since 1994. The information includes the personal identification number of the patient, drug names, number of units of the product sold, and the number of defined daily doses.

Cases of birth defects were identified through the National Patient Registry from January 1, 1996, through March 31, 2009. This registry contains individual patient-level data on all inpatients and outpatients encountered at hospitals and ambulatory care, including the personal identification number (that was used to link to the Medical Birth Registry), dates of admission and discharge, and diagnoses classified according to the International Classification System of Diseases.

3.2.3.2 Reviewer Comments:

The BDS and NBDPS databases that were used in the Slone/CDC study were based on patient self-reported data collected from surveys and the diagnostic information from the medical records. Patient participation was voluntary and the study samples are not nationally representative. It is unknown whether study participants are different from non-participants with regard to TPM exposure and types of birth defects.

Although the Wolters Kluwer Source Lx Patient database provides a large sample of patients who are demographically representative of the U.S. health care population, those patients are not nationally representative. The study outcomes were not validated by medical records. The prescription dispensing data may have over-estimated the rates of exposure by assuming that all individuals were 100% compliant with the prescriptions and used the medication until the last dose. As a result, a misclassification bias in exposure might have been introduced. Some confounding factors, such as family history of OCs, alcohol and tobacco use, substance abuse, and other important lifestyle risk factors, were not available to be adjusted for in this claims data analysis.

The Danish Medical Birth Registry and the National Patient Registry contain patient-level data on all inpatients and outpatients encountered in ambulatory care in

Denmark. However, data from the primary care setting were not included. According to the study's investigators, the fact that the cases were limited to those who were diagnosed at hospitals and in ambulatory care may have resulted in an under-estimation of the prevalence rate of major birth defects.

3.2.4 Study Population

3.2.4.1 Study Population:

Slone/CDC study:

- The base study population consisted of women who participated in the BDS and NBDPS studies.
- The cases were women whose babies had cleft lip with or without cleft palate, or isolated cleft palate, or MCMs.
- The controls were women whose babies were non-malformed.

Wolters Kluwer study:

- The base study population consisted of all women with medical claims relating to pregnancy and had medical data over the 13 months prior to birth and had linked infant data available for 12 months after birth.
- The TPM-exposed cohort included mother-baby pairs who were exposed to TPM at any dose, for any duration, and for any indication during pregnancy.
- The other AED control cohort included mother-baby pairs who were exposed to other AEDs for any indication during pregnancy.
- The epilepsy control cohort included women with a diagnosis of epilepsy who had no TPM exposure during pregnancy.
- The migraine control cohort included women with a diagnosis of migraine, but no epilepsy, no treatment during pregnancy with acute and preventive migraine drugs (APMD), and no TPM exposure during pregnancy.
- The migraine treated during pregnancy control cohort included women with a diagnosis of migraine treated during pregnancy with APMD, but no epilepsy and no TPM exposure during pregnancy.

- The diabetes control cohort included women with a diagnosis of type 1 or type 2 diabetes who had no TPM exposure during pregnancy and no history of epilepsy.

Denmark study:

- The base population consisted of women who had given live birth during the study time.
- The TPM-exposed cohort included women who were exposed to TPM during the first trimester of pregnancy.
- The unexposed control cohort included women who had no exposure to any newer-generation AEDs during the first trimester of pregnancy.

3.2.4.2 Reviewer Comments:

Recall bias of drug exposure, including TPM exposure, during pregnancy may exist in the Slone/CDC study since mothers in the control groups who had non-malformed babies may be less likely to recall their exposure to TPM during pregnancy compared to mothers of cases.

In the Wolters Kluwer study, multiple control cohorts were used to compare the relative risks (RRs) of MCMs and OCs associated with TPM exposure during pregnancy. Although the control cohorts of epilepsy, migraine, migraine treated during pregnancy, and diabetes were homogeneous subgroups of patients, the exposed cohort of interest, the TPM-exposed cohort is not. The TPM-exposed cohort consisted of women with TPM exposure at any dose, for any duration, and for any indication during pregnancy. Therefore, the RRs of OCs and MCMs associated with TPM exposure vs. these control cohorts are potentially confounded by the underlying conditions that was not the condition of the control cohort.

(b) (4)

The study population is appropriate in the Denmark study.

3.2.5 Exposures

3.2.5.1 Exposures:

Slone/CDC study:

- Exposure to TPM at any dose, for any duration, and for any indication during the first trimester of pregnancy

Wolters Kluwer study:

- Exposure to TPM at any dose, for any duration, and for any indication anytime during pregnancy
- Exposure to TPM at any dose, for any duration, and for any indication during the first trimester of pregnancy

Denmark study:

- Exposure to newer-generation AEDs, including TPM, at any dose, for any duration, and for any indication during the first trimester of pregnancy

3.2.5.2 Reviewer Comments:

The exposure definitions in the Slone/CDC study are appropriate. As OCs occur very early in the development of the fetus, it is important to restrict the exposure to TPM within the first trimester of pregnancy so that the time sequence, one of the criteria for the causal nature of an association, is met. Therefore, the risks in the Wolters Kluwer study were underestimated when the exposure data were anytime during the pregnancy because exposure occurred after the first trimester would not affect the development of OCs. The Qnexa teratogenicity report provide additional data for the Wolters Kluwer study on the prevalence rates of OCs and MCMs in children born to women exposed to TPM during the first trimester of pregnancy, which is more appropriate risk window for the assessment of TPM use and risk of OCs.

Another concern is that the risk attributable to TPM cannot be distinguished in the Wolters Kluwer study since the exposure was any exposure to TPM during pregnancy which included TPM monotherapy and/or polytherapy with other AEDs. In contrast, the

Slone/CDC study examined TPM monotherapy and the risk of OCs. The definition of "pregnancies" was based on the delivery date in the Wolters Kluwer study (first trimester was defined as from the earliest possible date of conception through 84 days following the latest possible date of conception, e.g., days 287 through 169 before the delivery date for singleton births at term), which may be subject to misclassification bias because of the nature of claims data. It is unclear how the researchers dealt with missing infant birth dates and ICD-9 codes for birth terms (pre-term, full-term, post-term).

The prescription dispensing data used in the Wolters Kluwer and the Denmark studies may have over-estimated the rates of exposure by assuming that all individuals were 100% compliant with the prescriptions and used the medication until the last dose. As a result, a misclassification bias in exposure might have been introduced. Another concern is that the exposure of interest in the Denmark study was newer-generation AEDs. It is unclear whether the exposure to TPM included TPM monotherapy and/or polytherapy with other AEDs. Lastly, as there were only 108 women exposed to TPM during their first trimester of pregnancy, the study power to examine the association between TPM exposure and risk of OCs and MCMs was limited.

3.2.6 Disease Outcomes of Interest

3.2.6.1 Study Outcomes:

Slone/CDC study:

- Cleft lip with or without cleft palate
- Isolated cleft palate

Wolters Kluwer study:

- MCMs
- Oral clefts

Denmark study:

- MCMs

3.2.6.2 Reviewer Comments:

In the Slone/CDC study, the study outcomes are specific types of oral clefts: cleft lip with or without cleft palate and isolated cleft palate. However, the other two studies used a general term of oral clefts and did not differentiate the cleft lip with or without cleft palate and isolated cleft palate. Since there may be differential diagnosis/ascertainment rates of cleft lip with or without cleft palate and isolated cleft palate and differential risks were observed from the Slone/CDC study (first-trimester use of TPM in monotherapy was found to be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate in the Slone/CDC study), the risk estimates in the Wolters Kluwer study and the Denmark study could be diluted by using the composite OCs as study outcome. Another concern for the Wolters Kluwer study is that the study outcomes were not validated by medical records, which could potentially bias the estimated relative risks toward the null due to potential non-differential misclassification of study outcomes.

The main outcome measure was all major birth defects in the primary analyses of the Denmark study. Subgroups of birth defects, e.g. OCs, were investigated in additional exploratory analyses. Infants with chromosomal aberrations, genetic disorders, and birth defects with known causes, such as fetal alcohol syndrome were excluded. The study outcomes were not validated in this study. However, it seems that validity of birth defect diagnoses through the national Patient Registry is high with a predictive value of 88% for birth defects overall⁷.

3.2.7 Study Covariates

3.2.7.1 Study Covariates

Potential confounders adjusted for in these three studies are listed in Table 1.

Table 1. Study covariates evaluated in each study

Potential Confounders	Slone/CDC Study *	Wolters Kluwer Study **	Denmark Study ***
Maternal age	√		√
Maternal obesity	√		
Maternal diabetes	√	√	
Folic acid intake	√		
Epilepsy	√	√	√
Migraine		√	√
Exposure to other AEDs		√	√
Maternal alcohol use	√		
Smoking	√		√
Maternal and family history of MCMs	√		
History of birth defects in siblings			√
Birth year	√		√
Mother's parity			√
Race	√		√
Geographic area	√		√
Level of mother's education			√
Level of mother's socioeconomic status			√

* In the Slone/CDC study, cases and controls were matched on birth year and region of birth. The pooled analysis additionally matched on study. Sensitivity analysis further matched, one by one, on folic acid intake, epilepsy, smoking, and other potential confounders. The results did not change meaningfully.

** In the Wolters Kluwer study, crude (unadjusted) relative risks were calculated comparing the prevalence rates of OCs and MCMs in the TPM-exposed cohort with each

comparator cohort, which include epilepsy cohort, migraine without treatment during pregnancy cohort, migraine with treatment during pregnancy cohort, and diabetes cohort.

*** In the Denmark study, the potential confounders were individually included in separate models with AED use and selected for the final adjusted regression models if they changed the prevalence odds ratios (PORs) by 10% or more. Maternal use of older-generation AEDs during the first trimester of pregnancy and maternal diagnosis of epilepsy were the only covariates that changed the PORs by 10% or more. Only these two covariates were included in the final analysis.

3.2.7.2 Reviewer Comments:

Ideally, all potential confounders should be included in multivariate analyses simultaneously to examine the independent effect of TPM exposure on OCs and MCMs. However, some data sources have incomplete or unavailable information on these study covariates. The Wolters Kluwer claims data do not contain information on many potential confounders. Even with the limited number of confounders available, the Wolters Kluwer study only calculated the crude relative risks.

The Slone/CDC study data are self-reported which may be subject to recall bias as well as reporting bias. Some patients with certain risk factors, such as smoking, alcohol abuse, and obesity may not report them. The Denmark study examined an extensive list of potential confounders and provided the adjusted relative risk of major birth defects associated with TPM exposure. However, some of the important potential confounders were not included in this study, such as, maternal diabetes, maternal obesity, folic acid intake, and maternal alcohol use.

3.2.8 Sample Size

3.2.8.1 Sample Size

Slone/CDC study:

In the Slone BDS database, 3 (0.39%) of 781 cases of cleft lip with or without cleft palate had TPM exposure during the first trimester of pregnancy compared with 2 (0.03%) of 6,935 controls. In the CDC NBDPS database, 4 (0.18%) of 2,260 cases of

cleft lip with or without cleft palate TPM exposure during the first trimester of pregnancy compared with 4 (0.05%) of 8,438 controls.

Wolters Kluwer study:

A total of 870 women were exposed to TPM during the first trimester of pregnancy.

Denmark study:

There were 108 women who had exposure to TPM during the first trimester of pregnancy.

3.2.8.2 Reviewer Comments:

None of the studies reported the *a priori* calculations of power for their analyses. In this case, the upper limit of the 95% confidence interval should provide a cap on the risk that a given study can exclude. However, estimates with wide confidence intervals are less reliable. The Denmark study acknowledged that the analyses of TPM were based on a limited number of exposures. The primary author of the Denmark study stated that “Topiramate use is rare in our cohort and the FDA warning on topiramate and clefts was published after we conducted our analyses and as such our study was not designed to evaluate this association. We only evaluated specific groups of birth defects in the context of any newer generation antiepileptic drugs and lamotrigine alone, where we had sufficient statistical power.” (Personal communication from Ditte Molgaard-Nielsen to Amy Egan on May 24, 2011)

3.2.9 Analyses

3.2.9.1 Analyses

Slone/CDC study:

Logistic regression models were used to compare first trimester use of TPM monotherapy vs. no use of AEDs between cases and controls matched on year and region of birth. Analyses were conducted separately on each database and on the pooled data, additionally matching on study. Sensitivity analyses were performed by further matching one by one on folic acid intake, epilepsy, smoking, and other potential confounders.

Wolters Kluwer study:

Crude (unadjusted) relative risks and 95% confidence intervals were calculated to compare the prevalence rates of OCs and MCMs in the TPM-exposed cohort with each comparator cohort.

Denmark study:

Logistic regression models were used to estimate the prevalence odds ratios of all MCMs with 95% confidence intervals. The odds ratios were adjusted for use of older-generation AEDs during the first trimester and maternal diagnosis of epilepsy.

3.2.9.2 Reviewer Comment:

A multivariate analysis adjusting for all study covariates simultaneously should be performed to estimate the independent effect of TPM exposure in the first trimester on OCs and MCMs. However, the Slone/CDC study adjusted for these study covariates by matching cases with controls on potential confounders, one by one, in a series of sensitivity analyses. Because of the lack of simultaneous adjustment, the reported risk estimates in this study might be affected by residual confounding. The Wolters Kluwer study only estimated crude relative risk without adjusting for potential confounders. The Denmark study evaluated the potential confounders by individually including them in separate models with AED use and selected for the final adjusted regression models if they changed the PORs by 10% or more. Maternal use of older-generation AEDs during the first trimester of pregnancy and maternal diagnosis of epilepsy were the only covariates that changed the relative risks by 10% or more and only these two covariates were included in the final analysis.

3.2.10 Study Results

3.2.10.1 Study Results

Slone/CDC study:

This study found that the median daily dose of TPM was 100 mg for both cases and controls (rang: 25-150 mg). As shown in Table 2, the odds ratio (OR) for MCM was 1.22 (95% CI, 0.19-13.01) in the Slone data and 0.92 (95% CI, 0.26-4.06) in the CDC data; for cleft lip with or without cleft palate, the OR was 10.13 (95% CI, 1.09-129.21) in

the Slone data and 3.63 (95% CI, 0.66-20.00) in the CDC data. The pooled OR was 1.01 (95% CI, 0.37-3.22) for MCM and 5.36 (95% CI, 1.49-20.07) for cleft lip with or without cleft palate. There was no case of isolated cleft palate in TPM-exposed pregnancies. The study concluded that first-trimester use of TPM monotherapy may be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate or overall MCM.

Table 2. Adjusted Odds Ratio and 95% Confidence Intervals for Topiramate vs. No AED Exposure in the First Trimester of Pregnancy by Study.

Study	Case/Control	Number of Mothers without any AED Exposure	Number of Mothers with Topiramate Exposure	Adjusted OR (95% CI)
Slone BDS	Control	6,933	2	Reference
	MCMs*	10,503	5	1.22 (0.19–13.01)
	CL/P**	778	3	10.13 (1.09–129.21)
CDC NBDPS	Control	8,434	4	Reference
	MCMs*	23,102	10	0.92 (0.26–4.06)
	CL/P**	2,256	4	3.63 (0.66–20.00)
Combined	Control	15,367	6	Reference
	MCMs*	33,605	15	1.01 (0.37–3.22)
	CL/P**	3,034	7	5.36 (1.49–20.07)

*MCMs: Major congenital malformations

**CL/P: Cleft lip with or without cleft palate

Wolters Kluwer study:

None of the relative risks (RR) of MCMs or OCs were statistically increased for the TPM-exposed cohort vs. each comparator cohort. The estimated relative risks for OCs and MCMs associated with TPM exposure anytime during pregnancy and during the first trimester of pregnancy were summarized in Tables 3 and 4, respectively. This study concluded that there was no significantly increased risk of OCs or MCMs with TPM exposure during pregnancy.

Table 3. Prevalence Rates of OCs and MCMs in Children Born to Women Exposed to TPM Anytime During Pregnancy

	n	Oral Clefts		MCMs	
		Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator	Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator
TPM	910	0.22	n/a	3.96	n/a
Other AEDs	4320	0.23	0.95 (0.21–4.33)	3.38	1.17 (0.82–1.67)
Epilepsy	2607	0.31	0.72 (0.15–3.37)	4.33	0.91 (0.63–1.32)
Migraine	26865	0.16	1.41 (0.34–5.80)	3.79	1.05 (0.75–1.45)
Migraine APMD*	3339	0.33	0.67 (0.15–3.00)	3.95	1.00 (0.70–1.44)
Diabetes	13063	0.26	0.84 (0.20–3.51)	6.58	0.60 (0.43–0.83)

* APMD: acute and preventive migraine drugs

Table 4. Prevalence Rates of OC and MCM in Children Born to Women Exposed to TPM during the First Trimester of Pregnancy

	n	Oral Clefts		MCMs	
		Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator	Prevalence Rate (%)	RR (95% CI) TPM vs. Comparator
TPM	870	0.23	n/a	4.25	n/a
Other AEDs	3615	0.17	1.39 (0.28–6.85)	3.21	1.33 (0.92–1.90)
Epilepsy	2607	0.31	0.75 (0.16–3.52)	4.33	0.98 (0.68–1.41)
Migraine	26865	0.16	1.47 (0.36–6.06)	3.79	1.12 (0.81–1.55)
Migraine APMD*	2526	0.24	0.95 (0.19–4.68)	4.32	0.99 (0.68–1.42)
Diabetes	13063	0.26	0.88 (0.21–3.67)	6.58	0.65 (0.47–0.89)

* APMD: acute and preventive migraine drugs

Denmark study:

As shown in Table 5, the adjusted prevalence odds ratio of major birth defects is 1.44 (95% CI, 0.58-3.58) for TPM-exposed vs. unexposed to any newer-generation AEDs. The study concluded that first-trimester exposure to newer-generation AEDs compared with no exposure was not associated with an increased risk of major birth defects.

Table 5. Association between First-Trimester Exposure to Newer-Generation AEDs and Major Birth Defects

First Trimester Exposure	No. of Women	No. (%) Birth Defects	Crude POR (95% CI)	Adjusted POR (95% CI)
None	836,263	19,911 (2.4)	1.0 (Reference)	1.0 (Reference)
AED*	1532	49 (3.2)	1.35 (1.02–1.80)	0.99 (0.72–1.36)
Topiramate	108	5 (4.6)	1.99 (0.81–4.88)	1.44 (0.58–3.58)
* lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam POR=prevalence odds ratio; CI=confidence interval; AED=antiepileptic drug				

3.2.10.2 Reviewer Comment:

As discussed previously, due to limited study power, the risk estimates from the Wolters Kluwer and the Denmark studies should be considered as exploratory and interpreted with caution. Because of the lack of simultaneous adjustment, reported risk estimates from the Slone/CDC study might be affected by residual confounding.

Since the Denmark study only provided the risk estimates for major birth defects, DEPI calculated the crude prevalence odds ratio of OCs associated with TPM exposure in the first trimester of pregnancy using the data provided in the Denmark study and the results were provided in Table 6. Please note the wide 95% confidence interval which suggests the inadequate sample size.

Table 6. Estimated crude prevalence odds ratio of oral clefts associated with first-trimester TPM exposure (data source: the Denmark study)


First Trimester Exposure	Number of Women	Number of Oral Cleft	Crude POR (95% CI)
Unexposed to any newer generation AED	836263	1421	Reference
Topiramate	108	1	5.45 (0.77-38.36)

4 DISCUSSION

4.1 COMPARISON BETWEEN THE SLONE/CDC & THE WOLTERS KLUWER STUDIES

The following is a summary of our comments concerning the inconsistent findings between the Slone/CDC and the Wolters Kluwer studies.

1. Compared to the Slone/CDC study where the exposure of interest was TPM monotherapy during the first trimester of pregnancy, the Wolters Kluwer study examined the association of any TPM use anytime during pregnancy and oral clefts. As the risk window for oral clefts is primarily in the first trimester, using TPM exposure that occurred anytime during pregnancy could have diluted the risk of TPM and bias the risk estimates towards the null in the Wolters Kluwer study. All risk estimates were higher in the analyses with TPM exposure only in the first trimester of pregnancy compared to those with TPM exposure anytime during pregnancy in the Wolters Kluwer study, which showed the importance of specifying an appropriate risk window for exposure.
2. The definition of "pregnancies" was based on the delivery date in the Wolters Kluwer study, which may be subject to misclassification bias because of the nature of claims data. It is unclear how the researchers dealt with missing infant birth date and ICD-9 codes for birth terms (pre-term, full-term, post-term).
3. It is not clear how the Wolters Kluwer study defined "oral clefts". It seems that this study did not differentiate the cleft lip with or without cleft palate and isolated cleft palate. Since there may be differential diagnosis/ascertainment rates of oral clefts with or without cleft palate and isolated cleft palate and differential risks were observed in the Slone/CDC study (first-trimester use of TPM in monotherapy was found to be associated with an increased risk of cleft lip with or without cleft palate, but not of isolated cleft palate in the Slone/CDC study), the risk estimates in the Wolters Kluwer study may be diluted.
4. The risk attributable to TPM cannot be distinguished in the Wolters Kluwer study since the exposure was any exposure to TPM during pregnancy which included TPM monotherapy and polytherapy with other AEDs. In contrast, the Slone/CDC study examined the risk of OCs with TPM monotherapy.

5. It is possible that the Wolters Kluwer study have missed some exposures and outcomes since they may not have all claims for these patients, which was acknowledged in their study posters.
6.  (b) (4)
7. Although the study results showed that the distributions of maternal age, ethnicity, and tobacco use were not balanced among the cohorts, the Wolters Kluwer study did not adjust the risk estimates for these confounding factors. However, based on the Slone/CDC study, the risk estimates did not change significantly when they adjusted one factor at a time for family history of birth defects, maternal age, race/ethnicity, pre-pregnancy BMI, smoking, alcohol, diabetes, folic acid intake, and epilepsy. Therefore, the impact of not adjusting for these risk factors on the risk estimates of Wolters Kluwer study is uncertain.
8. Lastly, cases in the Wolters Kluwer study were not validated. It is likely that the risk estimates are biased towards the null due to potential non-differential misclassification of study outcomes.

4.2 THE DENMARK STUDY

Although the Denmark study used nationwide data, only 108 women had exposure to TPM during the first trimester of pregnancy. It was not powered to examine the association between TPM exposure and risk of OCs. The adjusted prevalence odds ratios for TPM exposure and major birth defects provided by this study and the crude prevalence odds ratios for TPM exposure and OCs calculated by DEPI should be considered as exploratory analyses only. Another limitation is that cases from the primary care setting were not included in the study. Therefore, the prevalence rate of major birth defects may have been under-estimated in this study.

4.3 DIRECTION OF BIAS

The directions of bias associated with the study limitations in each study were summarized in Table 7.

Table 7. Study attributes and limitations and their potential impact on the association between TPM exposure during pregnancy and risk of OCs and MCMs

Direction of Bias	Slone/CDC Study	Wolters Kluwer Study	Denmark Study
Bias Towards No Association		<ul style="list-style-type: none"> • Over-estimation of exposure by assuming 100% compliance with prescriptions • Composite study outcome of oral clefts • Cases not validated • Small sample size • Misclassification of pregnancy based on delivery date 	<ul style="list-style-type: none"> • Over-estimation of exposure by assuming 100% compliance with prescriptions • Composite study outcome of oral clefts • Small sample size • Cases not validated
Bias Towards Positive Association	<ul style="list-style-type: none"> • Recall bias in reporting TPM exposure between cases and controls 		
Bias with Unknown Direction	<ul style="list-style-type: none"> • Confounding factors were not adjusted simultaneously • Reporting bias in reporting potential confounding factors, e.g., smoking, alcohol abuse 	<ul style="list-style-type: none"> • Confounding risk factors not adjusted • TPM monotherapy and polytherapy combined • (b) (4) 	<ul style="list-style-type: none"> • Maternal diabetes, obesity, folic acid intake, and alcohol use were not adjusted • TPM monotherapy and polytherapy combined • Cases limited to those who are diagnosed at hospitals and ambulatory care facilities

5 SUMMARY

In summary, each study has limitations, but with different directions of bias and significance. All three studies investigated the effect of TPM exposure during the first trimester of pregnancy on live birth infants. The fetal outcomes that ended in abortion (spontaneous or induced), or stillbirth could not be assessed. Overall, the Slone/CDC study provided higher risk estimates of OCs and MCMs associated with TPM exposure during the first trimester of pregnancy compared to the other two studies. The risks of OCs and MCMs were probably underestimated in the Wolters Kluwer study because most of the study limitations would bias the results towards no association between TPM

exposure during pregnancy and risk of OCs and MCMs. Those limitations along with the small sample size, might be responsible for the negative findings in the Wolters Kluwer study. The sponsor's comment that the Denmark study confirms an absence of a signal for an increased prevalence of MCMs with topiramate exposure is not supported because of the limited statistical power of the Denmark study.

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/s/

JING JU

01/20/2012

This review replaces the review dated December 28, 2011 by Jing Ju.

TAREK A HAMMAD

01/22/2012



**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: January 26, 2012

To: Members of the Endocrinologic and Metabolic Drugs Advisory Committee

From: Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology (OSE)

Subject: Risk Management Options

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

1 INTRODUCTION

This memorandum presents considerations for establishing a Risk Evaluation and Mitigation Strategy (REMS) for Qnexa (phentermine/topiramate) Controlled Release Capsules.

2 BACKGROUND

Vivus, Inc is seeking approval of Qnexa, a fixed-dose combination drug product containing two currently approved and available products, phentermine and topiramate, to treat adults with obesity. The Food and Drug Administration (FDA) previously issued a Complete Response letter on October 28, 2010 citing adverse cardiovascular effects and an insufficient assessment of Qnexa's teratogenic potential as safety reasons for not approving the application. The applicant resubmitted the application October 17, 2011. The applicant proposed to mitigate the risk of teratogenicity by contraindicating use for women of childbearing potential (WOCBP), and implement a Risk Evaluation and Mitigation Strategy (REMS) using restricted distribution to enforce this contraindication. The Agency believes the contraindication is too broad, and does not agree that, should Qnexa be approved, the risk of teratogenicity would outweigh Qnexa's benefits for every woman capable of becoming pregnant. Secondly, although it might be feasible to restrict use of Qnexa, such a restriction would not preclude use of the individual components of Qnexa by WOCBP for weight loss. Since the resubmission of the application, Vivus, Inc and the Agency have discussed possible approaches to mitigating the risk of teratogenicity. Given the availability of the separate ingredients of Qnexa, an ideal risk mitigation strategy is not apparent, although one option is proposed below.

Current availability of components of Qnexa

The individual components of Qnexa, topiramate and phentermine, have been available in the US since 1996 and 1959, respectively. Topiramate was first approved by the FDA in 1996 for the treatment of epilepsy, and subsequently received approval in 2004 for prophylaxis of migraine headaches. Fetal toxicity is included in the Topamax labeling in the *Warnings and Precautions*, *Use In Specific Populations*, and *Patient Counseling Information* sections of the labeling. Phentermine has been approved in the US since 1959, and is indicated as a short-term adjunct as part of a regimen of weight reduction. Phentermine is contraindicated for use during pregnancy. A REMS comprising a Medication Guide and a timetable for submission of assessments was required for topiramate to mitigate the risk of suicidality. This requirement was removed in June 2011, and no REMS is required currently for topiramate. A REMS has never been required for the marketing of phentermine.

FDAAA REMS Provisions

The Food Drug Administration Amendments Act (FDAAA) of 2007 authorizes the FDA to require pharmaceutical sponsors to develop and comply with REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies

beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all approved REMS for New Drug Applications (NDA) and Biologics License Applications (BLA) products have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling, and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (letters, drug fact sheets, etc) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

3 RISK MANAGEMENT CONSIDERATIONS

A variety of strategies are used to minimize risks associated with drugs and therapeutic biologics. These strategies minimize risks in a number of ways. They can communicate specific risk information, as well as information regarding optimal product use. In addition, they can provide guidance and/or encourage adherence to certain prescribing, dispensing, or monitoring requirements, and/or limit use of a product to only the most appropriate situations or patient populations.

If Qnexa is approved, a risk mitigation strategy (beyond labeling) is likely to be required to address the risk of teratogenicity. The following strategy would provide a mechanism to inform stakeholders about the risk, and would provide support to prescribers and patients to use Qnexa safely without causing undue burden on prescribers and patients using topiramate for other indications.

Proposed REMS Strategy

We are proposing that the REMS include the following elements.

- 1) A Medication Guide for patients that describes the risk of teratogenicity and provides patients with advice regarding safe use of the drug
- 2) A communication plan targeting prescribers likely to prescribe Qnexa, or its components, for weight loss. The communication plan would support implementation of the REMS, and would reach prescribers who do not opt to receive the training described below.
- 3) Elements to assure safe use that we propose to include:
 - a. Healthcare providers who prescribe Qnexa will receive training:
The sponsor would be responsible for ensuring that training is available to healthcare providers who choose to prescribe Qnexa; however, the training would not be a requirement for prescribing Qnexa. Training materials would support the risk-benefit discussion with WOCBP, and would provide advice about how to prevent fetal exposures.
 - b. Pharmacies that dispense Qnexa are specially certified:
The sponsor would be required to ensure that only certified pharmacies will dispense Qnexa. Certified pharmacies will be required to provide support to WOCBP, including reminding WOCBP to use contraception, reminding WOCBP to test for pregnancy, and ensuring that the patient receives the Medication Guide. Delivery options for patients to receive Qnexa would likely include shipment of Qnexa to the patients directly by a certified pharmacy or shipment to a pharmacy in the patient's locale for

pick-up.

- 4) An implementation system to ensure pharmacy certification is working as expected
- 5) A timetable for submission of assessments

Discussion of Proposed Strategy

We acknowledge that fetal exposures with Qnexa may occur if Qnexa is approved, even if a REMS with the proposed ETASU is put into place. The pregnancy prevention program in the Qnexa clinical trials mimicked other approved restricted distribution REMS programs instituted to prevent pregnancy exposures in patients taking teratogenic drugs. WOCBP were tested for pregnancy prior to beginning Qnexa, were counseled about pregnancy prevention, agreed to use double barrier or single barrier plus the oral contraceptive pill (OCP), and WOCBP were tested for pregnancy each month. Despite these efforts, there were 34 pregnancies during the clinical trial testing. In clinical testing, the pregnancies were discovered early in the pregnancy, at an average of 5.4 weeks gestation. Of the 19 pregnancies carried to term, no major malformations were found in the newborns.

Because the ingredients that comprise Qnexa are available without restriction for other indications, significant barriers to using Qnexa, including restricted distribution with mandatory pregnancy testing for Qnexa alone, would have limited impact. It is likely that some prescribers would prescribe the individual ingredients in an amount that would approximate Qnexa capsules to circumvent the requirements of the REMS.

FDAAA requires that the REMS not be unduly burdensome on patient access to the drug, considering in particular patients with serious or life-threatening diseases or conditions. Over 2 million patients receiving topiramate, most of whom are receiving topiramate for seizures or migraine prophylaxis, would be affected by restrictions placed on topiramate use.¹ A REMS required for Qnexa should not place undue burden on patients receiving topiramate for seizure disorders and prophylaxis of migraine headaches. At this time, a REMS is not required to assure that the benefits of topiramate exceed its risks for these indications, and any REMS established for Qnexa should not place undue barriers to access for these patients receiving topiramate for other indications.

The primary issue with requiring a REMS for Qnexa is the impracticality of establishing a restrictive REMS with mandatory elements, for example, mandatory pregnancy testing for WOCBP. Doing so would require that the monthly supply for WOCBP be held until pregnancy testing is conducted. To implement meaningfully this safe-use condition, it would be necessary to put general restrictions on the distribution of Qnexa, and perhaps

¹ Vicky Borders-Hemphill, Pharm.D., January 12, 2012. Review of Phentermine and Topiramate use in women of child-bearing potential. FDA/CDER/OSE Division of Epidemiology II (DEPI II).

also Topamax and topiramate, even for non-WOCBP. Although it might be preferable to institute a REMS for Qnexa that mandates monthly pregnancy testing for WOCBP, instituting a REMS with restricted distribution for Qnexa, Topamax, and topiramate is not possible without causing undue burden on patients receiving topiramate for seizure disorders and migraine prophylaxis. On the other hand, should restricted distribution be required of Qnexa, but not Topamax and topiramate, the REMS may be bypassed by prescribers using the individual components for weight loss. The extent that topiramate and phentermine might be prescribed to bypass a restrictive Qnexa REMS is not known.

4 CONCLUSION

FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. In considering a risk management program for Qnexa, FDA must keep in mind the need to minimize the burden on the healthcare system and the barriers to patient access while adequately managing the risks so that the benefits of Qnexa will outweigh the risks. A restrictive REMS is not practicable given the other serious indications for topiramate use, and the FDAAA requirement to refrain from creating undue burden on access for patients with serious illnesses. Your advice on the risk–benefit of Qnexa for the treatment of obesity should be made with the realization that the options for a restrictive REMS for Qnexa are limited.



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/
Supporting Document
Number:** 22-580/N-0056

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 October 17, 2011

Review Priority: Complete Response

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: Pooja Dharia

Background

The FDA Complete Response letter requested the submission of a one-year study, OB-305 (“Study 305”) which was a double-blind, placebo-controlled extension of 56-week study OB-303 (“Study 303”). Study 303 was reviewed as part of the original NDA submission. The objectives of extension Study 305 were to evaluate the safety and efficacy of Qnexa compared to placebo for the long-term treatment of obesity in adults with obesity-related co-morbid conditions who completed Study 303 at selected sites. The draft study protocol was not reviewed by FDA statisticians.

Design

Study 303 was a randomized, double-blind comparison of two fixed dose combinations of Qnexa (Phentermine/topiramate 15/92 mg, full dose; and PHEN/TPM 7.5/46 mg, mid dose) to placebo. Participation in extension Study 305 was determined by both site and patient characteristics from Study 303. While Study 303 was ongoing, the sponsor selected 37 sites out of the original 93 sites from Study 303 for participation in Study 305. The sites selected were those that generally had the largest numbers of patients who were compliant with all protocol requirements. Compliant patients at the selected sites were asked to participate in Study 305. Patients who agreed to participate were not re-randomized in Study 305 but instead continued their assigned treatment from Study 303 for a period of one year. The primary endpoint in Study 305 was the percent change in weight from Study 303 baseline (Week 0) to Week 108.

Results

Twenty-seven percent (27%) of patients originally randomized to Study 303 were enrolled in Study 305. The percentages of patients enrolling in Study 305 were unequal across treatment groups, with a lower percentage of eligible placebo patients enrolling (placebo 23%, Qnexa mid dose 31%, Qnexa full dose 30%). Twenty-three percent (23%) of patients randomized to Study 303 completed Study 305. Table 1 shows patient disposition for Studies 303 and 305.

Table 1. Patient disposition – Studies 303 and 305

	Full dose	Mid dose	Placebo	Total
<u>Study 303</u>				
Randomized	995 (100%)	498 (100%)	994 (100%)	2487 (100%)
Stopped med and visits	262 (26%)	124 (25%)	378 (38%)	764 (31%)
Stopped med and completed visits	99 (10%)	30 (6%)	52 (5%)	181 (7%)
Completed med and visits	634 (64%)	344 (69%)	564 (57%)	1542 (62%)
<u>Study 305 (selected sites)</u>	498 (50%)	249 (50%)	494 (50%)	1241 (50%)
Eligible to enroll	345 (35%)	194 (39%)	327 (33%)	866 (35%)
Enrolled	295 (30%)	154 (31%)	227 (23%)	676 (27%)
Completed med and visits	245 (25%)	127 (26%)	196 (20%)	568 (23%)

Figure 1 displays primary endpoint data across time in Study 303 for patients who completed study visits regardless of study medication compliance. Mean percent changes in weight from baseline to Week 56 are shown in separate panels by study medication compliance (stopped study medication vs. completed study medication). Patients who stopped their medication during the trial but continued study visits (n=181, Table 1) lost less weight than patients who completed the study on medication (n=1542). Only patients in the second panel and who also participated at selected sites were potentially eligible to enroll in Study 305.

Figure 1 Study 303: % change in weight (kg) from baseline to week 56 (end of Study) in patients who completed study visits

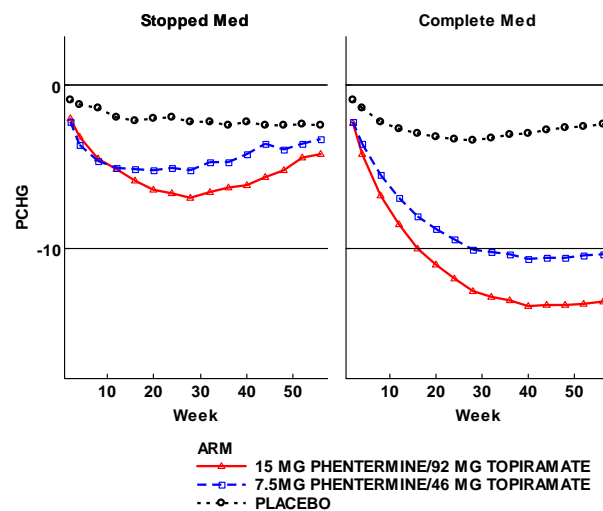


Table 3 (last line) shows sponsor's results for the primary endpoint, percent weight change from baseline to Week 108. The results on the primary endpoint were statistically significant for both Qnexa doses ($p < 0.001$).

Table 3 also shows two Study 303 patient cohorts defined by enrollment in Study 305 (no/yes) and presents corresponding percent changes in weight from baseline (Week 0) to Week 56. The mean baseline weight in Study 305 enrollees was approximately 4 kg less than that of patients not enrolled in Study 305 (107 kg vs. 103 kg). Also, compared to placebo, enrollees lost approximately 2 kg more weight at Week 56 compared to patients not enrolled (Qnexa full dose: 10 vs. 8 kg; Qnexa mid dose: 8 vs. 6 kg). Therefore Study 305 enrollees ended Study 303 at lower weights than did non-enrollees, having not only started at lower baselines but also having lost more weight than non-enrollees over the 56 weeks of Study 303. Specific estimates of treatment effect over 108 weeks must be interpreted in the context of substantial selection bias and loss to follow-up.

Table 2. % change in weight (kg) from baseline (ITT-LOCF): Least Squares Mean treatment differences between Qnexa and placebo

	Treatment group					
	Qnexa Full dose		Qnexa Mid dose		Placebo	
	N	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Cohort 1: Study 303 patients who did not enroll in Study 305						
Baseline (week 0)	686	107.1 (0.71)	334	106.3 (0.94)	752	107.6(0.70)
% change (week 56)		-8.5 (0.32)		-6.5 (0.42)		-0.8 (0.32)
Placebo difference (week 56)		-7.7 (0.36)		-5.6 (0.45)		-
Cohort 2: Study 303 patients who enrolled in Study 305						
Baseline (week 0)	295	103.0 (1.07)	153	103.6 (1.45)	227	102.1 (1.18)
% change (week 56)		-12.5 (0.48)		-10.3 (0.64)		-2.5 (0.52)
Placebo difference (week 56)		-10.0 (0.65)		-7.8 (0.77)		-
% change (week 108)		-10.5 (0.50)		-9.3 (0.67)		-1.8 (0.54)
Placebo difference (week 108)		-8.7 (0.67) *		-7.5 (0.80) *		-

LSM = least squares mean based on an ANCOVA model with treatment, gender, and diabetic status as fixed effects and baseline weight as a covariate

SE = standard error

* Primary endpoint, p<0.001 compared to placebo

Figure 2 displays monthly mean percent weight changes from baseline (Week 0) to Week 108 in patients who completed study medication and visits in Study 305 (23% of patients randomized to Study 303).

Figure 2 % change in weight (kg) from baseline (Week 0) to week 108 in Study 305 Completers

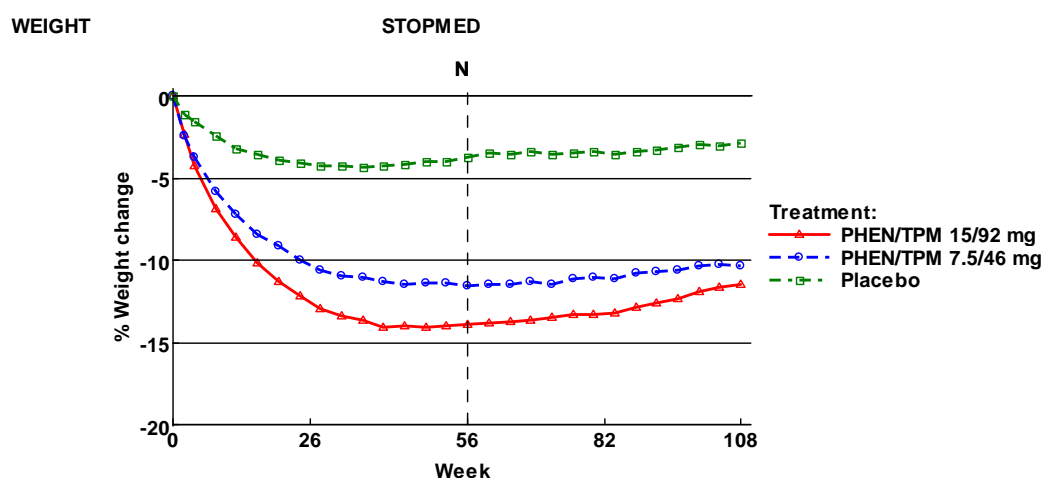
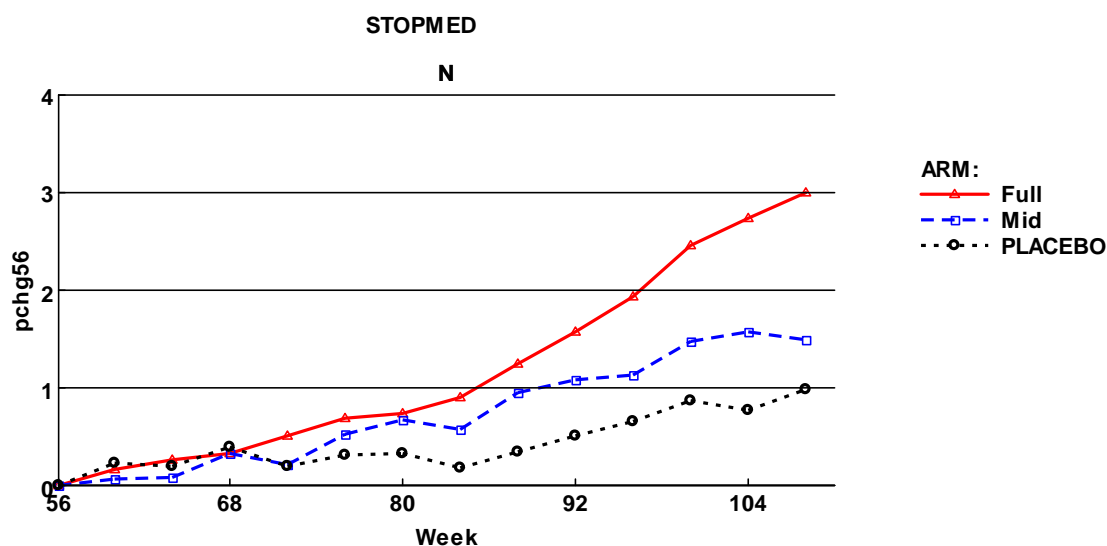


Figure 3 displays mean percent changes in weight from week 56 (Study 305 baseline) to subsequent weeks in study medication and visit completers. The figure shows a dose-related increase in weight over time and is consistent with Figure 2 and the LOCF data in Table 3.

Figure 3 Mean percent changes in weight (kg) from week 56 (Study 305 baseline) to subsequent weeks in Study 305 Completers



The Appendix shows longitudinal data out to Week 108 for selected safety endpoints (heart rate, blood pressure, lipids). All graphs show data for patients who completed study medication and visits to Week 108.

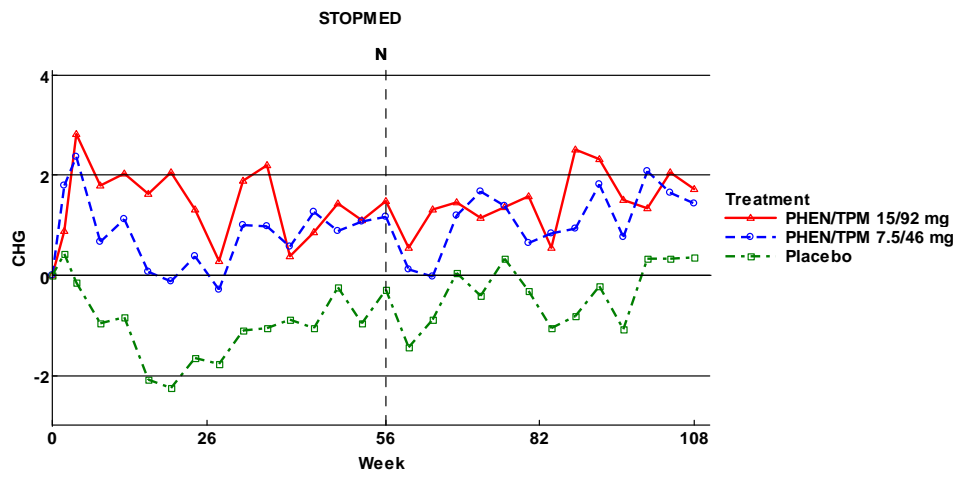
Summary

The objective of Study 305 was to evaluate the safety and efficacy of Qnexa compared to placebo in obese adults *who completed Study 303 at selected sites*. The sponsor enrolled patients in extension Study 305 by first selecting sites from Study 303 that generally had the largest numbers of patients who were compliant with all protocol requirements. The decision to select patients in the manner in which it was done contributed to several substantial limitations in the data. Although the study was statistically significant on the primary endpoint, percent change in weight from Study 303 baseline to week 108, the observed treatment differences over 108 weeks are most likely severely biased due to the selection method. The selected patients experienced lower mean baseline weights and greater mean weight reductions in Study 303 than did patients who did not enroll in Study 305. Among selected patients, it is doubtful that characteristics of placebo patients resembled those of Qnexa patients sufficiently to permit adequate between-treatment comparisons. Furthermore, Study 305 completers represented only 23% of patients originally randomized to Study 303. This substantial loss of follow-up data largely negates the statistical benefits typically conferred by randomization.

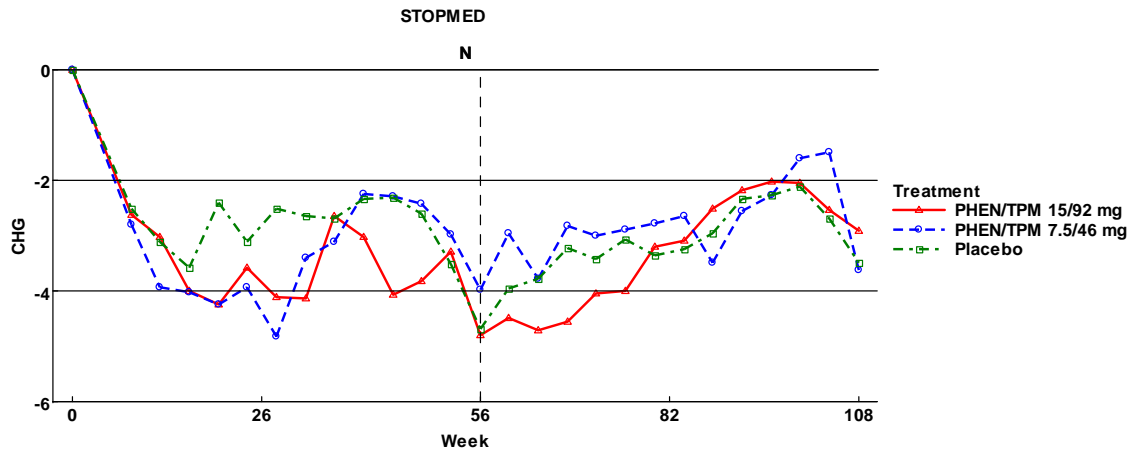
In conclusion, we consider the strength of the data in Study 305 to be equivalent to that of an observational finding.

APPENDIX

Heart Rate



DIABP



SYSBP

